INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY M4Q(R2)

Draft version
Endorsed on 14 May 2025
Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

M4Q(R2)
Document History

Code	History	Date
M4Q(R2)	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation.	14 May 2025

Legal notice: *This document is protected by copyright and may, with the exception of the ICH logo, be used, reproduced, incorporated into other works, adapted, modified, translated or distributed under a public license provided that ICH's copyright in the document is acknowledged at all times. In case of any adaption, modification or translation of the document, reasonable steps must be taken to clearly label, demarcate or otherwise identify that changes were made to or based on the original document. Any impression that the adaption, modification or translation of the original document is endorsed or sponsored by the ICH must be avoided.*

The document is provided "as is" without warranty of any kind. In no event shall the ICH or the authors of the original document be liable for any claim, damages or other liability arising from the use of the document.

The above-mentioned permissions do not apply to content supplied by third parties. Therefore, for documents where the copyright vests in a third party, permission for reproduction must be obtained from this copyright holder.

ICH HARMONISED GUIDELINE

THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY

M4Q(R2)

ICH Consensus Guideline

TABLE OF CONTENTS

SCOPE AND ORGANISATION

The M4Q(R2) guideline establishes the location and structure of quality information for registration applications of all medicinal products for human use. It supports various submission types, including those referring to or consisting of master files, and applies to both initial marketing authorisation and post-approval submissions. This guideline is structured to be flexible to accommodate all types of medicinal products and their components.

The applicant should consult applicable ICH and regional guidelines, including those for master files, to determine the appropriate sections and content for their specific product. Any non-applicable sections should be left out. Illustrative examples included in the guideline are meant to further clarify location of potentially relevant content but are not exhaustive and should not be interpreted as requirements.

The M4Q(R2) structure is presented in a globally harmonised format with sufficient granularity to facilitate digitalisation and organised for easy access, analysis, and knowledge management. This granularity also supports inclusion of information from emerging concepts, such as advanced manufacturing, use of structured data management processes, artificial intelligence/machine learning, bioinformatics, and advanced analytical tools. The applicant should include applicable information on these tools within the relevant sections of the dossier pertinent to their specific application. Novel processes or technologies that directly impact product quality may be described in greater detail to ensure clarity and comprehension.

The M4Q(R2) guideline organises information across Module 2.3 and Module 3 in a complementary manner. Module 2.3 serves as the basis for regulatory assessment and facilitates lifecycle management, however it does not supersede regional post approval change requirements. Module 2.3 provides for a sufficiently comprehensive overview and evaluation of the medicinal product and its components applying science- and risk-based principles. Module 2.3 includes sections for general information (2.3.1), overall development and control strategy (2.3.2), core quality information (2.3.3), and development summaries and justifications (2.3.4). Additionally, Module 2.3 may include product lifecycle management information (2.3.5) and product quality benefit-risk considerations (2.3.6). Module 3 serves as a repository for detailed descriptions of methods, data, and other relevant quality information that supports Module 2.3. Information in 2.3.1, 2.3.2, 2.3.4, 2.3.6, and Module 3 is supportive. The applicant may amend or supplement the information for post-approval submissions.

The quality information for materials of the medicinal product is organised within corresponding sections across Module 2.3 and Module 3.2. These sections are aligned with the roles of these components, including Drug Substances (DS), Substance Intermediates (SI), Raw Materials (RM), Starting Materials (SM), Reference Standards/Materials (RS), Excipients (EX), Impurities (IM), Drug Products (DP), Product Intermediates (PI), Packaged Medicinal Products (PM), Pharmaceutical Products (PH), and Medical Devices (MD). These sections are further organised using the following structure: Description, Manufacture, Control, and Storage:

- Description: Identifies the material and its key characteristics;
- Manufacture: Outlines the production process and process controls;
- Control: Describes quality control measures such as specifications;
- Storage: Provides container closure system, stability, storage condition, and retest period/shelf life.

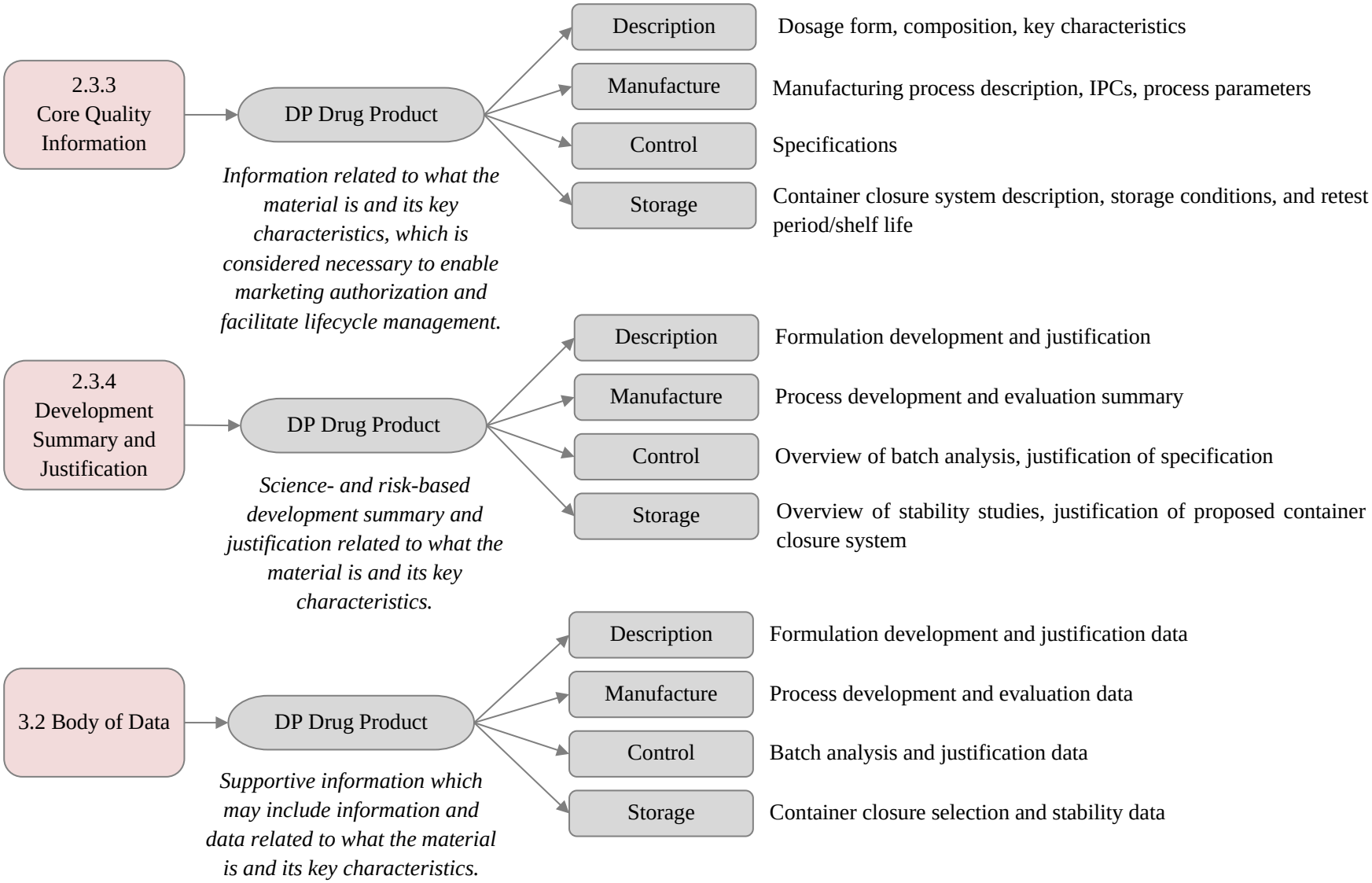
This structure ensures consistency and efficiency of information management. Figure 1 illustrates the relationships among 2.3.3 Core Quality Information, 2.3.4 Development Summary and Justifications, and Module 3.2 Body of Data in the context of the structure used for materials.

Sections not directly tied to material information adopt a different categorisation and header logic. This allows for flexibility in presenting information relating to Analytical Procedures and Facilities, with direct explanations provided within relevant sections.

Section headers may include mandatory keywords in parentheses ( ) or optional keywords in square brackets [ ] to uniquely identify a section's content and distinguish between multiple instances.

ICH M4Q(R2) aims to foster harmonisation of the quality dossier content, ideally enabling the submission of a single M4Q(R2) version of the dossier across countries or regions. When a country or regional requirement cannot be avoided due to legal obligations, the applicant may provide additional information specific to the country or region directly in the relevant section.

Figure 1: Illustration of relationships among sections 2.3.3 Core Quality Information, 2.3.4 Development Summary and Justifications, and Module 3.2 Body of Data in the context of DMCS Model used for materials.



MODULE 2. COMMON TECHNICAL DOCUMENT SUMMARIES

2.3. Quality Overview

2.3.1 General Information

The following information should be provided, when applicable:

- non-proprietary or common name of the drug substance(s);
- non-proprietary or common name of the drug product(s);
- dosage form(s) and drug release profile(s);
- strength(s) and the form of the drug substance for the expression of strength;
- route(s) and methods of administration;
- primary packaging;
- medical device(s) or any co-packaged item(s);
- maximum daily dose.

A schematic representation of the product's configuration (e.g., a picture) may be included to illustrate the product components and their functional relationships.

2.3.2 Overall Development and Overall Control Strategy

This section provides a high-level overview of the medicinal product's development and control strategy, aiming to facilitate understanding and supporting an efficient assessment. The Overall Control Strategy (OCS) is built upon the concepts defined in ICH Q8 considering the patient's needs and reflects the Core Quality Information. This section includes:

- Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) (2.3.2.1);
- Overall product development strategy (2.3.2.2); and
- Representation of how the individual control strategies contribute to the OCS (2.3.2.3).

For the submission of restricted part of, or stand-alone master file for material (e.g., drug substance), an overall development strategy and a representation of the overall control strategy should be provided (ICH Q8, Q11).

The information in this section may be updated throughout the product lifecycle to reflect any relevant changes in the Core Quality Information (CQI).

2.3.2.1 Quality Target Product Profile

The QTPP should be provided (ICH Q8).

2.3.2.1.1 Critical Quality Attributes

A list of the CQAs should be provided, preferably in a tabulated format, with a brief justification for their selection. When necessary, a cross-reference to other subsections of 2.3.4 may be included (ICH Q6A/Q6B, Q8, Q9, and Q11).

2.3.2.2 Overall Development Strategy

This section should provide a concise overview of the development rationale to help

contextualise the development strategy, highlighting the pivotal decisions made along the development to achieve the intended quality.

This overview serves as a high-level introduction to how the CQAs were used to guide drug substance, product, and process development, in line with ICH Q8 and Q11 guidelines. Cross-references may be included to more detailed information in 2.3.4 or Module 3.

Where applicable, the use of an enhanced approach, including the establishment of design space, as well as prior knowledge and platform technologies should be briefly discussed, illustrating how these resources were used for the development process. While not intended as an exhaustive summary, this discussion should provide enough details to understand the reasoning behind key development choices, particularly those that affect multiple aspects of product design.

2.3.2.3 Overall Control Strategy Representation

The OCS is a holistic and integrated approach encompassing considerations from the CQAs to the end-to-end controls, describing how the individual control strategies interact to ensure product quality (ICH Q6A/Q6B, Q8, Q9, Q10, and Q11). A representation, such as a table, diagram, or flowchart of the proposed OCS should be included. This representation may cross-reference other sections of Module 2.3 (e.g., 2.3.3 CQI).

The OCS should address the manufacturing process from the introduction of starting/source materials to the final drug product, including packaging. The OCS may also address the pharmaceutical product after transformation and any device to be used with the drug product, where relevant to ensure product quality or performance.

The OCS should cover the control strategies only for the material(s) (e.g., drug substance) included in the application or submission.

For applications referring to master file(s), the information provided by the master file holder (e.g., the open part of a master file) should be considered. If applicable, relevant information, such as specifications and manufacturing processes, should be incorporated into the OCS.

2.3.3 Core Quality Information

The applicant should describe the information considered necessary to support a science- and risk-based regulatory assessment to enable marketing authorisation and facilitate lifecycle management. This section should include all information subject to lifecycle management per regional post-approval change requirements to ensure product quality.

The applicant should maintain the CQI throughout the product lifecycle to ensure that product quality information remains current. When Established Conditions (ECs) per ICH Q12 are approved, lifecycle management activities should follow the approved Product Lifecycle Management Document (PLCM) in 2.3.5.2. However, the identification of ECs should not result in a reduction of information submitted in the marketing authorisation application.

2.3.3.DS Drug Substances

(Drug Substance Name) [Manufacturer]

The information for each drug substance or manufacturing site should be organised following the guidelines specified in this section. The applicant may repeat this section as needed. If the information for each manufacturing site is the same, there is no need to repeat the sections.

2.3.3.DS.D Description

(Drug Substance Name) [Manufacturer]

2.3.3.DS.D.1 Nomenclature

This section should include information on the nomenclature of the drug substance, such as recommended international non-proprietary name (INN), regional non-proprietary name (e.g., USAN, BAN, JAN), WHO Reference Number, company code, Chemical Abstracts Service (CAS) registry number, compendial name, and other chemical names.

2.3.3.DS.D.2 Structural characteristics

This section should include the structural characteristics of the drug substance, based on the nature of the substance.

For chemical entities, this section should include, for example, the structural formula, including relative and absolute stereochemistry, the molecular formula, confirmation of structure based on synthetic route, spectral analysis, and the relative molecular mass.

For biologics, this section should include, for example, relevant structural characteristics, including a description of the molecular structure, the schematic amino acid sequence indicating glycosylation sites or other posttranslational modifications, and relative molecular mass. The degree and profile of structural heterogeneity of the biologically active variants should also be illustrated.

2.3.3.DS.D.3 General properties

This section should include a summary of general properties of the drug substance and their impact on the CQAs of the drug product.

For chemical entities, these properties may include, for example, selected crystalline form, pH, ionic strength, particle size distribution, hygroscopicity, and solubility.

For biologics, a description of biological activities and immunological properties should be included, where relevant.

2.3.3.DS.M Manufacture

(Drug Substance Name) [Manufacturer]

2.3.3.DS.M.1 Description of the manufacturing process

This section should include sufficient information on the drug substance commercial manufacturing process along with a flow diagram/process schematic, which represents the sequence of unit operations and the scale of production, including substance intermediate(s), if applicable. The diagram should indicate points of sampling at which in-process controls (IPCs), intermediate tests, or final drug substance controls are conducted. If applicable, the applicant should identify the unit operations conducted in batch mode or in a continuous manufacturing process, any process models utilised, and describe the proposed design space, if any (ICH Q8, Q13).

Batch size/scale, starting/source materials, aseptic processing procedures, and intermediates should be defined.

For chemical entities, this section should include chemical structures in the diagram/schematic

and quantities of raw materials.

For biologics, this section should include intermediates and their holding times, and major equipment.

For sterile drug substances, a description of the method of sterilisation along with appropriate acceptance criteria should be included.

For continuous manufacturing, aspects that are not typically associated with batch processes should be provided, including equipment design and dimensions (ICH Q11, Q13).

Any reprocessing steps should be identified and included in the process flow diagram (ICH Q7).

2.3.3.DS.M.2 Process controls

This section should include process parameters and in-process controls that are essential for ensuring that a drug substance of the required quality will be produced consistently. The information should include associated test methods (with cross-references to the relevant analytical procedures 2.3.3.AP) and control ranges/acceptance criteria, organised per unit operation.

When models are associated with the process parameters and IPCs, a description/identification of the models used should be included in 2.3.3.AP.

2.3.3.DS.C Control

(Drug Substance Name) [Manufacturer]

This section should include the specification(s) for the drug substance, including tests, name of the analytical procedures, and acceptance criteria for release and/or retest period/shelf life with applicable standards/pharmacopeia(s). Cross-references to relevant Analytical Procedures sections should be provided, including any proposed real time release testing (RTRT) approach (ICH Q6A/Q6B, Q11, Q14, M7).

When models are associated with the analytical procedures for release and/or stability testing of the drug substance, this section should include a description/identification of the models used in 2.3.3.AP.

2.3.3.DS.S Storage

(Drug Substance Name) [Manufacturer]

2.3.3.DS.S.1 Container closure system

This section should include information about the container closure system proposed for the bulk material (biologics) and drug substances. Specifications for primary packaging material and for functional secondary packaging materials that are critical to drug substance quality should be included (ICH Q11).

2.3.3.DS.S.2 Stability, storage conditions, and retest period/shelf life

This section should include information about the proposed retest period/shelf life and storage conditions. The post-approval stability protocol and stability commitment should be included (ICH Q1/Q5C).

For biological bulk material and drug substance, storage conditions, shelf life, and shipping conditions should be specified. If applicable, the traceability (chain of custody and chain of identity) should be included.

2.3.3.SI Substance Intermediates, if Applicable

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

This section should include information for substance intermediates with established specifications. For intermediates controlled through in-process controls, the applicant should provide this information in 2.3.3.DS.

For most chemical entities, only 2.3.3.SI.C will be populated.

For biologics (e.g., the antibody used for an antibody drug conjugate or viral vectors used for *ex vivo* gene modified Advanced Therapy Medicinal Products (ATMPs)), information should be provided for Description, Control, and Storage, as applicable. The applicant may provide the Manufacture information separately or integrated into 2.3.3.DS.M.

This section may be used to describe the manufacture of specific substance intermediates separately from the main drug substance manufacturing process. This may be relevant for highly complex end-to-end biological drug substance manufacturing processes or cases where the sub-part of the end-to-end drug substance manufacturing process, up to a specific substance intermediate, is performed by a different manufacturer.

2.3.3.SI.D Description

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

If applicable, this section should include information on the description of the substance intermediate to the same level of detail as under each corresponding heading in 2.3.3.DS.D.

2.3.3.SI.M Manufacture

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

For a substance intermediate manufactured by the same manufacturer and as part of the drug substance manufacturing process, an integrated manufacturing process description should be presented under 2.3.3.DS.M. This information should be provided separately in this section only if deemed necessary and the content should align with 2.3.3.DS.M.

2.3.3.SI.C Control

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

This section should include specification(s) for the substance intermediate(s) and references to relevant analytical procedures. If applicable, a description of any proposed RTRT approach should be included (ICH Q6A/Q6B, Q11, Q14).

2.3.3.SI.S Storage

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

If applicable, this section should include information on the container closure system, stability, storage conditions, retest period/shelf life, and shipping conditions to the same level of detail as under each corresponding heading in 2.3.3.DS.S.

2.3.3.SM Starting/Source Materials

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

This section should include information in accordance with guidelines specified (ICH Q5A, Q5B, Q5D, Q11).

2.3.3.SM.D Description

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

This section should include a description of the starting/source material which allows for unambiguous identification (e.g., chemical structure, molecular weight), as appropriate. If the starting/source material is biologically sourced (e.g., a cell bank, or cells used in manufacture of allogeneic or autologous ATMPs), information on its source should be provided.

2.3.3.SM.M Manufacture

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

Where appropriate, this section should include information on the manufacturer/supplier of the starting materials.

For biological starting materials, information on the procedures used to generate new Working Cell Banks (WCB)/seed lots, and/or cell modification procedures should be provided, if applicable. Generation of Master Cell Banks (MCB) should be described in 2.3.4.SM (ICH Q5B, Q5D).

Information about how animal/human-derived materials are obtained (e.g., procurement information, manufacturing process) should be included.

2.3.3.SM.C Control

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

This section should include specifications for starting/source materials with a cross-reference to 2.3.3.AP, as appropriate. Testing information should be provided for cell banks/seed lots. For animal or human-derived starting materials, information about control of adventitious agents of the starting/source materials, including donor eligibility screening and testing for ATMPs, should be provided, as appropriate (ICH Q5A). If applicable, the applicant should discuss control of adventitious agents in 2.3.4.IN.2.2.

2.3.3.SM.S Storage

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

This section is typically not needed for chemical entities. If applicable, storage information may be provided.

For biological starting/source materials, information on the container closure system, stability storage conditions, retest period/shelf life, and shipping conditions should be included, as appropriate. When applicable, a description of the cold chain logistics should be provided.

2.3.3.RM Raw Materials

[Raw Material Name] [Drug Substance Name] [Manufacturer] [Intermediate Substance Name]

This section should include information on raw materials used in the drug substance and substance intermediate manufacturing processes. Information on multiple raw materials may be presented in a single tabular format, as appropriate.

2.3.3.RM.D Description

[Raw Material Name] [Drug Substance Name] [Manufacturer] [Intermediate Substance Name]

This section should include information on the raw materials (e.g., name, where in the process it is used, function).

2.3.3.RM.M Manufacture

[Raw Material Name] [Drug Substance Name] [Manufacturer] [Intermediate Substance Name]

This section is typically not required for chemical raw materials. If applicable, manufacturing information may be provided.

For biological raw materials, manufacturing and/or source information relevant to adventitious agent control should be included (ICH Q5A).

2.3.3.RM.C Control

[Raw Material Name] [Drug Substance Name] Manufacturer] [Intermediate Substance Name]

The applicant should refer to compendia or provide specifications for raw materials in line with the control strategy (ICH Q11). For biological raw materials, information essential to the control of adventitious agents of the materials should be included, as appropriate (ICH Q5A). If applicable, the applicant should discuss control of adventitious agents in 2.3.4.IN.2.2.

2.3.3.RM.S Storage

[Raw Material Name] [Drug Substance Name] [Manufacturer] [Intermediate Substance Name]

For chemical raw materials, this section is typically not required. For biological raw materials, this section may include storage information.

2.3.3.EX Excipients

[Excipient Name] [Drug Product Name] [Manufacturer]

This section should include information on excipients used in the manufacture of the finished dosage form.

For compendial excipients, information may be presented in a single tabular format including their function and reference to relevant standards.

For novel excipient(s), this section should include full details of description, manufacture, control, and storage, with cross-references to supporting safety data (nonclinical and/or clinical).

2.3.3.EX.D Description

[Excipient Name] [Drug Product Name] [Manufacturer]

For novel excipients or non-compendial excipients that might directly impact drug product performance, (e.g., release controlling agents, adjuvants), a detailed description should be provided in this section. If applicable, the description should include the characteristics that correlate to the drug product's CQA. If the excipient is formulated or consists of a mixture of compounds, the qualitative and, whenever possible, quantitative composition should be specified.

2.3.3.EX.M Manufacture

[Excipient Name] [Drug Product Name] [Manufacturer]

Where appropriate, e.g., for novel excipients, this section should include a general outline of the manufacturing process and controls relevant for the CQAs of the drug product.

2.3.3.EX.C Control

[Excipient Name] [Drug Product Name] [Manufacturer]

For compendial excipients, specifications additional to the compendia reference(s) should be included, as appropriate.

For novel or non-compendial excipients, this section should include specifications with a cross-reference to 2.3.3.AP, as appropriate.

For biological excipients, information on the control of adventitious agents should be included, as appropriate (ICH Q5A). If applicable, the applicant should discuss control of adventitious agents in 2.3.4.IN.2.2.

2.3.3.EX.S Storage

[Excipient Name] [Drug Product Name] [Manufacturer]

Where applicable, e.g., for novel excipients, this section should include information on the container closure system, storage conditions, and retest period/shelf life.

2.3.3.RS Reference Standards and/or Materials

[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]

This section should include information on the reference standard(s) and/or material(s) used for testing of drug substance, drug product, substance intermediate, and product intermediate, when necessary (ICH Q6A/Q6B). Information on multiple reference standards may be provided in a single tabular format, as appropriate.

2.3.3.RS.D Description

[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]

This section should include nomenclature and structural features, as appropriate (ICH Q6A/Q6B).

2.3.3.RS.M Manufacture

[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]

For chemical reference standards and/or materials, this section is typically not required. For biological in-house reference materials, this section should include manufacturing/purification information (e.g., process description or a cross-reference to relevant sections), if applicable (ICH Q6A/Q6B).

2.3.3.RS.C Control

[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]

This section should include a list of specifications with references to compendial methods or cross-references to 2.3.3.AP. For biological in-house reference materials, additional information such as calibration (against e.g., primary/international standards) or qualification procedures may be provided, if applicable (ICH Q6A/Q6B).

2.3.3.RS.S Storage

[Reference Standard Name] [Manufacturer] [Drug Substance Name] [Drug Product Name]

For biological in-house reference materials, this section should include the storage conditions, use period, and the container closure system.

2.3.3.DP Drug Products

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

The applicant should organise information in this section in a systematic manner to include core quality information for each drug product constituent (e.g., isotope, lyophilized powder and diluent/solvent). This section may be repeated as needed.

2.3.3.DP.D Description

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

This section should include a description of the finished dosage form including its type, qualitative and quantitative composition, and overages/overfills, if applicable. A list of all excipients with their name, function, references to their quality standards, and their amounts on a per-unit basis should be provided in a tabular format. Where relevant, this section should include the reference strength of the active moiety/entity if it differs from the drug substance strength. A brief description of the container closure system (primary and functional secondary packaging) used for the finished dosage form should be included. Any special design features of the drug product should be identified (ICH Q8).

2.3.3.DP.M Manufacture

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

When multiple manufacturers are involved in the manufacturing of the drug product, the applicant may repeat some of these subsections as needed. If the information for each manufacturing site is the same, there is no need to repeat the sections.

2.3.3.DP.M.1 Batch formula

This section should include a definition of the batch size and the batch formula for batches (ICH Q8, Q13). A batch formula should include a list of all components of the finished dosage form to be used in the manufacturing process; their amounts on a per batch basis, including any overages; and a reference to their quality standards.

2.3.3.DP.M.2 Description of the manufacturing process

This section should include sufficient information on the drug product commercial manufacturing process along with a flow diagram/process schematic, which represents the sequence of unit operations and the scale of production, including product intermediate(s), if applicable. The diagram should indicate steps where materials enter and/or exit the process and points of sampling at which IPCs, testing of intermediates, or final product controls are conducted. If applicable, the applicant should identify the unit operations conducted in batch mode or in a continuous manufacturing process, any process models utilised, and describe the proposed design space, if any (ICH Q8, Q13).

When an integral device is utilised, the drug product manufacturing process description should include the assembly steps of the drug product and medical device/medical device component.

A list of the type of equipment used should be included. For major equipment that has an impact on product quality, additional information, such as design, operating principle, and/or size should be provided.

For products intended to be sterile, the method of sterilisation for the drug product (including primary packaging material sterilisation, if applicable) along with appropriate acceptance criteria should be included. If the primary packaging is a pre-sterilised device, the applicant

should include information about sterilisation in 2.3.3.MD.M.

If applicable, reprocessing steps should be identified and included in the process flow diagram.

2.3.3.DP.M.3 Process controls

This section should include process parameters and IPCs that are essential for ensuring that a drug product of required quality is produced consistently. The section should include associated test methods (with cross-references to relevant Analytical Procedures sections) and control ranges/acceptance criteria, organised per unit operation. When models are associated with process controls of the drug product, the applicant should present information of the models used in 2.3.3.AP.

2.3.3.DP.C Control

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

This section should include the specification(s) for the drug product, including tests, name of the analytical procedures, and acceptance criteria for both release and shelf life with applicable standards/pharmacopeia(s). Cross-references to relevant Analytical Procedures sections should be provided, including any proposed RTRT approach (ICH Q6A/Q6B, Q8, Q14, M7).

When models are associated with the analytical procedures for release and/or stability testing of the drug product, this section should include a description/identification of the models used in 2.3.3.AP.

For the controls performed on the product after transformation (e.g., appearance after reconstitution) and for the controls related to device functionalities, the appropriate release and shelf-life specifications should be included in this section. Specifications that are not part of the release or stability testing of drug product, e.g., for compatibility/in-use after transformation, should be included in 2.3.3.PH.C.

2.3.3.DP.S Storage

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

2.3.3.DP.S.1 Container closure system

This section should include information about the container closure system including materials of construction proposed for bulk product, if applicable, and drug product (ICH Q8). Specifications for primary packaging material and functional secondary packaging material should be included.

2.3.3.DP.S.2 Stability, storage conditions, and shelf life

This section should include information about the proposed storage conditions and shelf life. This storage information may cover in-use, short-term excursions, and shipping. The information for each of the proposed container closure system(s) used for bulk product (if applicable) and drug product should be provided. The post-approval stability protocol and stability commitment may be provided (ICH Q1/Q5C).

For biologics, if applicable, this section should include traceability (chain of custody and chain of identity).

2.3.3.PI Product Intermediates, if Applicable

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

This section should provide information for product intermediates with established specifications. The applicant should provide information for Description, Control and Storage as applicable.

2.3.3.PI.D Description

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

This section should include identification and composition (if applicable), of each product intermediate, including a list of all excipients with their name, function, and references to their quality standards, to the same level of detail as in 2.3.3.DP.D.

2.3.3.PI.M Manufacture

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

If the product intermediate is manufactured separately, this section should include the batch formula, which includes a list of all components of the product intermediate, their amounts, and a reference to their quality standards.

The applicant may provide the Manufacture information integrated into section 2.3.3.DP.M or separately, if deemed necessary (e.g., different manufacturer, different manufacturing process) and the content should align with 2.3.3.DP.M, as applicable.

2.3.3.PI.C Control

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

This section should include specification(s) for the product intermediate and references to relevant analytical procedures. If applicable, a description of any proposed RTRT approach should be included (ICH Q6A/Q6B, Q8, Q14).

2.3.3.PI.S Storage

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

This section should include information regarding the container closure system, stability, storage conditions, holding time/shelf life to the same level of detail as under each corresponding heading in 2.3.3.DP.S. Additionally, shipping conditions may be provided.

2.3.3.MD Medical Devices, if Applicable

(Medical Device Name) [Manufacturer]

This section should be used when regional requirements mandate that the elements pertaining to the medical device should be submitted as part of a medicinal product application. This may include cases where:

- the medical device and/or device part and the medicinal product form an integral product intended exclusively for use in the given combination, which is not reusable and where the action of the medicinal product is principal;
- the medical device is packed together with the medicinal product (sometimes called “co-packaged”);
- the product information refers to a specific medical device to be used with the medicinal product, and the medical device is obtained separately by the user of the medicinal product (sometimes called “referenced”).

This section should include information relevant for the device or the device constituent(s) before it encounters the medicinal product. The applicant should place information relating to the device once combined with the medicinal product (e.g., compatibility of the device with the formulation or changes in the device design and operating characteristics during the medicinal product development) in the relevant sections as follows:

- In the *DP* (drug product) section in case of an integral device if no transformation is required.
- In the *PM* (packaged medicinal product) section in case of co-packaged or referenced device, leading to the medicinal product being a multiconstituent product.
- In the *PH* (pharmaceutical product after transformation) section in case of an integral, co-packaged, or referenced device intended to be used in combination with the pharmaceutical product after transformation.

If applicable, this section should include confirmation that the device has been assessed and authorised for use as medical device. Such confirmation may replace part or most of the information described in these medical device sections.

Software information should be included in this section when information on medical device software is required per regional regulations. Software in scope of this guideline may include, for example, software that is classified as an integral medical device, or as components or accessories of a medical device.

2.3.3.MD.D Description

(Medical Device Name) [Manufacturer]

This section should include a description of the medical device covering aspects relevant for the medicinal product quality, safe use, and performance. This may include dimensions, principles of operation, functionalities, and/or a visual representation of the device. If applicable, the critical components or accessories of the device should also be described.

If applicable, this section should include the device risk classification according to the (regional) regulatory classification system, as well as evidence (e.g., certificate) that the device has been assessed and authorised for use as medical device in compliance with regional requirements.

In case of use of software as a medical device, the name, major version, and description of its purpose may be provided.

2.3.3.MD.M Manufacture

(Medical Device Name) [Manufacturer]

This section may include a description of the manufacturing process of the device or device parts. A list of process parameters impacting the device's performance, with their associated values, should be provided. For devices intended to be sterile, an appropriate method of sterilisation should be mentioned.

2.3.3.MD.C Control

(Medical Device Name) [Manufacturer]

This section should include the specifications of the medical device or device constituent parts that are not fully assembled into a device. This may include dimensions and operating conditions.

If applicable, this section should include software specifications appropriate to confirm compliance with regulatory, cybersecurity, and interoperability requirements.

2.3.3.MD.S Storage

(Medical Device Name) [Manufacturer]

If applicable, this section may include the shelf life/re-test period, storage conditions, and packaging of the medical device.

2.3.3.PM Packaged Medicinal Products for multiconstituent products, if Applicable

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

This section should include information about the marketing pack(s) for medicinal products that contain constituents (individually packaged in primary container) and that are subsequently packaged together in a secondary container or in a unit as a marketing pack. For example, a vial with a powder for solution may be packaged together with a syringe, or several primary packaged drug products may be packaged together in a marketing pack.

2.3.3.PM.D Description

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

This section should include the configuration description. A description of functional secondary packaging may be provided.

2.3.3.PM.M Manufacture

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

If the secondary packaging process directly affects product quality, this section should include a description of the process for packaging the separately packaged constituents into the final container, as appropriate.

2.3.3.PM.C Control

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

This section may include release and shelf-life specifications. If information about any separately packaged constituent is not included in 2.3.3.DP or 2.3.3.MD section, the specifications for this separately packaged constituent should be included in this section.

2.3.3.PM.S Storage

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

2.3.3.PM.S.1 Container closure system

If functional secondary packaging is applied, specifications should be provided.

2.3.3.PM.S.2 Stability, storage conditions, and shelf life

This section should include the storage conditions and shelf life, if different from those of its individual constituents, cross-referencing the storage section(s) of 2.3.3.DP and/or 2.3.3.MD, as appropriate. Information for in-use and shipping may be provided. The post-approval stability protocol and stability commitment may be provided (ICH Q1).

2.3.3.PH Pharmaceutical Product after transformation, if Applicable

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

This section should include information in situations where the finished dosage form needs

transformation into its administrable dosage form (e.g., dilution, dissolution, dispersion, suspension, or reconstitution).

2.3.3.PH.D Description

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

This section should include the details of transformation of the drug product including composition or composition range of pharmaceutical product after transformation, as appropriate.

2.3.3.PH.M Manufacture

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

Not applicable.

2.3.3.PH.C Control

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

This section is intended to cover additional controls that may be appropriate after product transformation and prior to use, or for tests conducted to confirm in-use quality requirements.

This section may include tests that are not conducted at the time of release or on stability and do not need to be part of routine tests (such as compatibility/in-use after transformation).

The applicant should not duplicate information for release and stability specification of parameters to be performed for pharmaceutical product after transformation that is already mentioned in 2.3.3.DP.C.

2.3.3.PH.S Storage

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

2.3.3.PH.S.1 Stability, storage conditions, and shelf life

This section may include the in-use storage condition and in-use period, as appropriate. The stability protocol or a summary in case of any planned post-approval stability study may be included.

2.3.3.AP Analytical Procedures

(Analytical Procedure Name or code) [Purpose] [Material Type]

This section should be used to identify all non-compendial procedures by, at a minimum, the name or the code of each procedure, the material(s) for which it is used, and the purpose of the test. Compendial procedures should be referenced where they are used (e.g., in control sections of the different materials), however compendial procedures that are adjusted by the applicant are expected to be presented in this section. An overview table containing all non-compendial procedures and adjusted compendial procedures used in the control strategy (e.g., release, stability, IPC) for the different materials may be provided.

For each procedure, this section should include an appropriate description or tabulated version of the analytical procedures according to principles defined in ICH Q14. When models for multivariate analytical procedures are associated with the analytical procedures, a description of that model should also be presented. When RTRT is used, the description of the corresponding analytical procedure should be included.

The level of detail should be commensurate with the nature and risk of the material.

2.3.3.FA Facilities

[Manufacturer]

This section should include the name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing of drug substance, drug substance intermediates, drug product, and drug product intermediates. Regional guideline may describe expectations for the content of this section in more detail.

2.3.4 Development Summary and Justification

This section should describe how the drug substance and product, their components, if applicable, and manufacturing process were developed, including the main choices made throughout the development. This section should include science- and risk-based justifications, including discussion of the proposed commercial process and control strategy, and when ICH Q12 is applied, the justification of ECs and reporting categories, if applicable. The applicant may include a discussion of relevant prior knowledge, such as platform technology experience, as well as knowledge or experience from other similar products, available to the applicant together with justifications of its applicability to the product in the marketing authorisation application. The content of this section is supportive. The applicant may amend or supplement the information due to post-approval submissions. Information in Module 3 may be cross-referenced to support the discussion as needed.

The 2.3.4 sections of a drug product and drug substance will also cover the materials used in drug substance/drug product manufacture (e.g., raw materials, excipients, substance intermediate, and product intermediates). In cases where one or more of these materials has undergone a separate development, the applicant may use a separate section 2.3.4 for this material with the corresponding DMCS structure (e.g., 2.3.4.SI Substance Intermediate, 2.3.4.RM Raw Material, 2.3.4.EX Excipients, or 2.3.4.PI Product Intermediate). Subsections and content should match 2.3.4.DS/DP sections, as appropriate. The applicant should not repeat the information in section 2.3.4.DS or 2.3.4.DP.

2.3.4.IN Integrated Development and Justifications

This section is used for the justification of topics when a holistic discussion across several parts of the dossier is advantageous, e.g., across drug substance to drug product. The corresponding Core Quality Information is provided in relevant subsections of 2.3.3 and the corresponding data and supportive information in Module 3.2, where the topic is addressed as specified below.

2.3.4.IN.1 Overview of changes during development

This section may present a tabular overview of the changes during development, the reason for each change, and the batches used for clinical and nonclinical studies. Appropriate justifications should be included in relevant subsections of 2.3.4 with data and supportive information in Module 3.2. The applicant should provide cross-references to the location of studies in other sections or modules of the CTD that are used to assess the impact of changes on the drug substance(s) and corresponding drug product(s) (ICH Q5E, Q8, Q9, Q10, Q11).

2.3.4.IN.2 Integrated discussions

This section contains end-to-end justifications, as appropriate. The applicant can apply the DMCS structure as appropriate. The applicant should not repeat justifications included here in

2.3.4.DS or 2.3.4.DP.

2.3.4.IN.2.1 Integrated justifications of extractables and leachables

This section should include a comprehensive summary of the assessment of the potential risks associated with extractables and leachables. Information submitted in this section should be cross-referenced to the following: 1) relevant subsections in 2.3.4 which provide justification for the selection of materials, manufacturing systems, container closure systems, and device components; 2) relevant subsections of 2.3.3 where the actual controls are delineated; 3) appropriate Module 3.2 subsections which contain supportive information and data; and 4) appropriate Module 4 sections providing safety data and supportive information.

2.3.4.IN.2.2 Integrated justifications of control of adventitious agents

This section should describe the integrated justification assessing the risk of adventitious agents (ICH Q5A, Q5D, Q6A/Q6B). Development work, including testing done during development (e.g., viral clearance studies) should be discussed. If applicable, the results of clearance studies as part of the justification of the integrated control strategy of adventitious agents should be summarised. The integrated justification should cross-reference the specific quality requirement and controls for raw/starting/source materials and the manufacturing process included in 2.3.3. The data and information from the studies should be provided in the corresponding materials subsection in Module 3.2.

For non-viral adventitious agents, an integrated justification on the avoidance and control of these agents, such as transmissible spongiform encephalopathy agents, bacteria, *Mycoplasma*, and fungi should be provided. This justification may include, for example, certification and/or testing of raw materials, excipients, or other materials, as well as justification around relevant control of the manufacturing process, as appropriate for the material, process, and agent.

For viral adventitious agents, an integrated justification on the avoidance and control of viral contamination should be provided. Viral safety studies should demonstrate that the materials used in manufacturing are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing and material sourcing are suitable.

2.3.4.IN.2.3 Development and justifications for products without a defined and/or isolated drug substance

This section should summarise the development and justification of the commercial manufacturing process and its control strategy for products without a defined and/or isolated drug substance (e.g., integrated drug substance and drug product continuous manufacturing or some ATMPs). The applicant should apply the DMCS structure and include all relevant descriptions and justifications, such as those related to cell line or starting materials, manufacturing (including an overview and the process design), and formulation. The applicant should provide justification for viral vectors used for *ex vivo* genome modification of cellular ATMPs in 2.3.4.SI. The applicant should not repeat justifications included in this section in 2.3.4.DS or 2.3.4.DP.

The applicant should include CQI in the relevant 2.3.3 section. For example, for cellular ATMP that are gene-modified with a viral vector, viral vector CQI should be included in 2.3.3.SI and information on description, manufacturing, and formulation of the product in 2.3.3.DP. The data and supporting information should be included in the corresponding 3.2 section (ICH Q3A-Q3E, Q5A-Q5E, Q6A/Q6B, Q13, M7).

2.3.4.IN.2.4 Integrated justifications of specific items (Optional)

The applicant may choose to justify the control strategy in this section where an end-to-end justification is of significant advantage. The applicant may repeat this section for specific uses (e.g., integrated justification of specifications, mutagenic impurities, residual solvents, and elemental impurities). The CQI or data and supportive information should be provided in the corresponding material subsections in 2.3.3 or 3.2, respectively (ICH Q1/Q5C, Q3A-Q3E, Q5A-Q5E, Q6A/Q6B, M7).

2.3.4.IN.3 Equivalency, similarity or sameness with a reference product

2.3.4.IN.3.1 Summary and Justifications of analytical and in vitro similarity with a reference product, if Applicable

The applicant should explain the choice of reference product, including justification if samples of the reference product have been acquired from another region, when such an approach is acceptable according to regional requirements.

For a generic product or other follow-on to a chemical entity (e.g., abridged/abbreviated application), an overview of how the *in vitro* equivalency with the reference product is demonstrated should be included. It may include biowaiver approaches. Details should be provided in 2.3.4.DP.D, 2.3.4.DP.M and/or in 3.2.DP, as appropriate.

For a biosimilar product, the applicant should delineate the strategy for biosimilarity assessment, provide a summary of the results of the biosimilarity studies, and justify biosimilarity with the reference product. Data and information should be provided in 3.2.DP.D.

2.3.4.IN.3.2 Summary and Justifications of sameness with a product approved in a reference country, if a reliance procedure is used

The applicant should discuss and declare sameness of the medicinal product with the product approved in the reference country, according to regional guidelines. The applicant should explain and justify any difference.

2.3.4.DS Drug Substances

(Drug Substance Name) [Manufacturer]

The information for each drug substance or manufacturing site should be organised following the guidelines specified in this section and may be repeated in this section as necessary to accommodate multiple drug substances or manufacturing sites. If the information for each manufacturing site is the same, there is no need to repeat the sections.

2.3.4.DS.D Description

(Drug Substance Name) [Manufacturer]

A summary of the studies performed to characterise and confirm the drug substance structure and its general properties, including physicochemical and biological properties should be provided in this section. The level of detail should be commensurate with the nature of the substance, whereby a greater level of detail may be appropriate for highly complex substances.

2.3.4.DS.M Manufacture

(Drug Substance Name) [Manufacturer]

2.3.4.DS.M.1 Development of manufacturing process and process controls

This section should include information on how the manufacturing process was developed to establish the commercial manufacturing process capable of consistently producing drug substance of the intended quality (ICH Q11).

For biologics, the proposed batch scale up may be discussed, as applicable (ICH Q11).This section should describe the risk assessment approach(es) used and summarize how the conclusions from the risk assessment(es) were used to justify the manufacturing process development (ICH Q11).

Information should be included if modelling is used as part of the manufacturing and process controls.

For sterile drug substances, the applicant should justify the chosen method of sterilisation.

For biological drug substances, the applicant should discuss and justify clearance steps (for product- and process-related impurities). Viral clearance studies should be discussed in 2.3.4.IN.2.2.

This section should include information on the development and characterisation of the process controls, including how the process parameters and IPCs and their ranges were identified (ICH Q11). Information should be included if modelling is used as part of the control strategy.

When an enhanced approach is used, this section should discuss the impact of the manufacturing process on the CQAs, understanding of the relationship between input and outputs, justification of process ranges/acceptance criteria for inputs and outputs, and design space, if applicable (ICH Q11).

2.3.4.DS.M.2 Changes during manufacturing process development

This section should discuss significant changes to the manufacturing process of the drug substance used to produce nonclinical / clinical batches (as appropriate) and batches proposed for commercial distribution (ICH Q11).

2.3.4.DS.M.3 Comparability for multiple manufacturing sites

In the case of more than one proposed commercial manufacturing site, this section should provide comparative information and discuss the impact of any differences between the sites on the drug substance quality and consistency.

2.3.4.DS.M.4 Summary of process validation or evaluation studies

This section should include summaries and conclusions of the process validation and or evaluation studies. Process validation for non-sterile chemical entities may not be necessary at the time of application.

This section should include justification for processes where manufacturing equipment is intended to be reused.

If raw materials (e.g., solvent) are intended to be recycled or regenerated, a justification should be included.

For biologics, a justification for holding times and storage conditions for intermediates should

be included (ICH Q5C).

A justification for any reprocessing steps for the product type should be included according to ICH Q7.

2.3.4.DS.C Control

(Drug Substance Name) [Manufacturer]

2.3.4.DS.C.1 Control of impurities

For chemical entities, this section should summarise the actual and potential impurities most likely to occur during the synthesis, purification, and storage of the drug substance, with a comprehensive risk assessment. Any potential impurity that may impact the quality of the drug substance, including those originating from starting/source materials, raw materials, and substance intermediates, should be discussed as part of the risk assessment. The applicant should also cross-reference the associated data provided in 3.2.IM and provide the rationale for the reporting and control of impurities (ICH Q3A, Q3C, Q3D, M7). If an integrated discussion is needed, the applicant may consider using 2.3.4.IN.2.4.

For biologics, information about product and process-related impurities should be provided (ICH Q6A/Q6B). For the control of product and process-related impurities, subsections for each identified impurity may be included.

2.3.4.DS.C.2 Batch analysis

This section should include a tabulated overview of batches, listing the batch number, batch size/scale, date of manufacture, manufacturing site, manufacturing process (biologics), and use (e.g., stability, nonclinical, and clinical). A discussion on conformance to specifications and justification of trending should be included, as appropriate.

2.3.4.DS.C.3 Justification of specifications

This section should include justification for release and stability specifications, including the rationale for the quality attributes to be tested and CQAs not tested, if any. Compliance to any standard/pharmacopeia(s) should be specified. The rationale for skip-testing/non-routine testing for the drug substance should be included.

A rationale for relevant changes to specifications throughout development should be provided, which may include a reference to other sections discussing development aspects (e.g., 2.3.4.DS.M, 2.3.4.AP), as appropriate.

If RTRT approach is adopted, a justification for the approach should be included (ICH Q6A/Q6B, Q11, Q13, Q14, M7).

2.3.4.DS.S Storage

(Drug Substance Name) [Manufacturer]

2.3.4.DS.S.1 Container closure system

This section should include justification for the proposed container closure system, including primary and functional secondary packaging components that are critical to drug substance quality.

The justification should include reasons for the choice of materials. It should also address safety

of materials of construction and compatibility of the material(s) of construction with the drug substance, including potential interactions between drug substance and container (e.g., sorption to container and leaching) cross-referencing 2.3.4.IN.2.1.

2.3.4.DS.S.2 Stability, storage conditions, and retest period/shelf life

An overview of the stability and a justification for storage condition and retest period/shelf life for the proposed container closure system of the drug substance should be provided. The approach for calculating the drug substance retest period/shelf life should be justified. If extrapolation is proposed, this section should include a justification for the approach used to calculate the drug substance retest period/shelf life (ICH Q1).

A summary of the studies conducted and the conclusions of these studies with respect to storage conditions and shelf life should be provided (ICH Q1).

For biological bulk material and drug substance the shipping conditions should be justified.

2.3.4.SM Starting/Source Materials

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

This section should be used as needed to provide justifications for starting materials in accordance with relevant guidelines (ICH Q5A, Q5B, Q5D, Q11, Q11 Q&A). The DMCS structure may be applied, as appropriate.

2.3.4.SM.D Description

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

This section should include information on selection of the starting material(s), as appropriate (ICH Q11 Q&A).

For cell banks, this section should include information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated into the initial cell clone used to develop the MCB (ICH Q5B, Q5D).

2.3.4.SM.M Manufacture

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

For chemical entities starting materials that are not commercially available, this section should include a manufacturing process flow of the starting material, if applicable, to help justify the controls applied to the starting material (ICH Q11 Q&A).

For biological starting materials, this section should include information on the establishment of the MCB, the WCB, or the virus seed/bank system, as applicable (ICH Q5B, Q5D).

2.3.4.SM.C Control

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

This section should include a justification of specifications for starting materials, as applicable (ICH Q5B, Q5D, Q11, Q11 Q&A).

2.3.4.SM.S Storage

[Starting Material Name] [Drug Substance Name] [Intermediate Substance Name]

For biological starting materials, justifications for storage/shipping conditions, as well as proposals for monitoring of stability should be included (ICH Q5B, Q5D).

2.3.4.RS Reference Standards and/or Materials

(Reference Standard Name) [Manufacturer]

This section should include information on the characterisation of reference standards/materials. If distinct reference standards/materials are developed for process/product related impurities, their appropriateness should be discussed. For biological in-house reference materials, this section should summarize results of calibration or qualification of current and historical in-house reference materials, as well as a justification of the appropriateness of the storage conditions, use period, and container closure system, if applicable. The applicant may apply the DMCS structure as appropriate.

2.3.4.DP Drug Products

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

The applicant may repeat this section as needed, for example, to include the development information of each drug product or a diluent/solvent that is part of the packaged medicinal product.

2.3.4.DP.D Description

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

2.3.4.DP.D.1 Components of the drug product

This section should discuss the development studies supporting the choice of excipients, including their concentration, amounts, quality, and functional characteristics that can influence the drug product performance relative to their respective functions.

The compatibility between the drug substance(s) and excipients should be discussed. Additionally, key physicochemical characteristics of the drug substance may be discussed, as appropriate, such as water content, solubility, particle size distribution, polymorphic or solid-state form (with a cross-reference to specific information provided under 2.3.4.DS.D) that can influence the drug product performance.

When a device is used in direct contact with the drug product, either as part of or as the primary container closure system, the choice of the device and its compatibility with the formulation (integral devices) should be discussed.

2.3.4.DP.D.2 Formulation development

This section should include information on the development studies conducted to establish the dosage form and the formulation (ICH Q8, Q9). The development of the dosage form and formulation for drug product, taking into consideration the proposed route of administration and usage should be discussed. Where relevant, this section should include the reference strength or chemical or physical form (e.g., salt form, stereoisomer or polymorphic form) of the active moiety/entity if it differs from the drug substance strength or form. If applicable, the rationale for any special design features and how they affect the drug product should be discussed.

A discussion of any overages in the formulation should be included with a justification concerning the safety and efficacy of the product in terms of the reason and amount of overage, if applicable.

2.3.4.DP.D.3 Comparability during formulation and product development

This section should discuss differences between clinical formulations and the proposed commercial formulation (i.e., composition, dosage form) and provide justification to support the level of change. Where applicable, the bridging strategy, including results of comparative *in vitro* studies (e.g., dissolution) or a summary and reference to comparative *in vivo* studies (e.g., bioequivalence), should be provided as appropriate (ICH M9, M13).

This section may include a discussion of any change in the device design and operating characteristics (for integral devices) during product development. It should cover how these changes may impact safety, and/or performance and/or instructions for use of the overall product. Where relevant, it should explain any differences between the study device and its commercial form.

2.3.4.DP.D.4 Physicochemical and biological properties of drug product

This section may include physicochemical and biological properties 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.

2.3.4.DP.D.5 Microbiological attributes

As appropriate, this section should discuss the microbiological attributes of the proposed dosage form, including, for example, the selection and effectiveness of preservative systems in products containing antimicrobial preservatives.

2.3.4.DP.M Manufacture

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

2.3.4.DP.M.1 Development of manufacturing process and process controls

This section should provide information on how the manufacturing process was developed to establish the commercial manufacturing process capable of consistently producing drug product of the intended quality. The approach(es) followed for risk assessment should be described and the conclusions used to justify the manufacturing process development should be summarised. The proposed batch scale up may be discussed, as applicable (ICH Q8). For sterile products, the chosen method of sterilisation should be justified.

Information on the development and characterisation of the process controls should be provided, including summaries of the studies that describe how the parameters and in-process controls and their ranges were established (ICH Q8).

A discussion of the impact of the manufacturing process on the CQAs, understanding of the relationship between the inputs and outputs, justification of process ranges/acceptance criteria for inputs and outputs, and design space, if applicable, should be included when an enhanced approach is used (ICH Q8).

If modelling is used as part of the manufacturing and process controls, relevant information should be included.

2.3.4.DP.M.2 Changes during manufacturing process development

This section should discuss the significant changes to the manufacturing process and/or

manufacturing site of the drug product used to produce registration/pilot, nonclinical, clinical batches, and batches intended for commercial distribution, as applicable. Information should be presented in a way that facilitates comparison of the processes and the corresponding batch analysis information under 3.2.DP.C (ICH Q8). The data from comparative analytical testing on relevant drug product batches used to determine the impact on quality of the drug product (and/or intermediate, as appropriate) should be summarised.

2.3.4.DP.M.3 Comparability for multiple manufacturing sites

In the case of more than one proposed commercial manufacturing site, this section should provide comparative information and discuss the impact of any differences between the sites on the drug product quality and consistency.

2.3.4.DP.M.4 Summary of process validation or evaluation studies

This section should include summaries and conclusions of the process validation and/or evaluation studies, as applicable. Justification and relevant information should be provided if a continuous process verification approach is used (ICH Q8).

Processes where manufacturing equipment (e.g., sterile filters) is intended to be reused should be justified.

Justification for where or which raw materials (e.g., solvent) are intended to be reused, recycled, or regenerated should be included.

Holding times and storage conditions for intermediates may be justified (ICH Q1).

A discussion and justification of any reprocessing procedures, including criteria for material reprocessing, may be included.

2.3.4.DP.C Control

(Drug Product Name) [Manufacturer] [Manufactured Dosage form] [Strength]

2.3.4.DP.C.1 Control of impurities

This section should summarise the actual or potential impurities most likely to occur during drug product manufacturing and storage (due to interaction with excipients, solvents and/or container closure system). Any potential impurity that may impact the quality of the drug product, including those originating from product intermediates, should be discussed as part of the risk assessment for actual and potential impurities. The applicant should cross-reference the associated data provided in 3.2.IM.

A summary and conclusion of the performed risk assessment may be included (ICH Q3B, Q3C, Q3D, Q3E, Q5C, Q6A/Q6B, M7). If an integrated discussion is needed, the applicant may consider using 2.3.4.IN.2.4.

2.3.4.DP.C.2 Batch analysis

A tabulated overview of the batches listing the batch number, batch size/scale, date of manufacture, manufacturing site, manufacturing process, and use (e.g., stability, nonclinical, clinical) should be presented. Conformance to the specification and justification of trending should be discussed, as appropriate.

2.3.4.DP.C.3 Justification of specifications

A justification of release and stability/shelf-life specifications should be provided, including the rationale for the quality attributes to be tested and CQAs not tested, if any. Compliance with any standard/pharmacopeia(s) should be specified.

If applicable, the rationale for skip-testing for the drug product should be included (ICH Q6A/Q6B). Any justification for the controls performed on the product after transformation should cross-reference 2.3.4.PH.C.

As appropriate, this section should include information about relevant changes to specifications throughout development, which may include a reference to other sections discussing development aspects (e.g., 2.3.4.DP.M, 2.3.4.AP).

If RTRT approach is adopted, the approach should be justified (ICH Q6A/Q6B, Q8, Q13, Q14, M7).

2.3.4.DP.S Storage

(Drug Product Name) [Manufacturer] [Manufactured Dosage form] [Strength]

2.3.4.DP.S.1 Container closure system

This section should include the choice and rationale used to select the container closure system(s) for the commercial products (ICH Q8).

For bulk product, suitability of the container closure system may be discussed.

For drug product primary packaging materials, this section should discuss the suitability of the container closure system, including the suitability for the patient needs, and should justify the choice of materials with respect to the impact on product quality. The discussion should include a summary of studies performed to demonstrate the integrity of the container and closure to prevent microbial contamination and possible interactions between product and container closure system. The justification should include, for example, choice of materials, compatibility of the material(s) of construction with the finished dosage form, including sorption to container and leaching (cross-referencing 2.3.4.IN.2.1), and safety of materials of construction.

For drug product functional secondary packaging material, the rationale for choice of packaging material should be discussed.

2.3.4.DP.S.2 Stability, storage conditions, and shelf life

This section should provide an overview of the stability studies (including short-term studies) and justification for storage condition/shelf life and/or holding time for each of the proposed container closure system(s) used for the bulk product (if applicable) and for the drug product (including for device constituents utilised as primary container closure system).

If extrapolation is proposed, this section should include a justification for the approach used to calculate the drug product shelf life (ICH Q1).

Summaries and conclusions of the studies for in-use, handling, and shipping may be included.

2.3.4.MD Medical Devices, if Applicable

(Medical Device Name) [Manufacturer]

2.3.4.MD.D Description

(Medical Device Name) [Manufacturer]

This section should discuss the device design. The level of detail that should be included depends on the type and complexity of the device and the risk associated with its use for the intended purpose.

This section should include an assessment of biocompatibility to ensure safety according to relevant standards. Extractables study outcome should support the selection of the device, as applicable.

A summary of information relating to usability/human factor studies may be presented.

If applicable, software functional requirements, including software architecture, interfaces, and algorithms should be defined.

2.3.4.MD.M Manufacture

(Medical Device Name) [Manufacturer]

Depending on the risk inherent to the device and its use in the medicinal product, this section may include a description of the manufacturing process development for the device and, where relevant, of its accessories or separate parts, including software. A discussion of the selection of materials and components used in the device may be included. If applicable, the discussion should demonstrate the compatibility of components with relevant regulatory requirements.

When the device or device components undergo sterilisation before becoming a constituent of the medicinal product, a justification of the sterilisation method selection regarding its compatibility with the device materials and intended use should be provided.

2.3.4.MD.C Control

(Medical Device Name) [Manufacturer]

The specifications applied to the device, based on the intended use, and relevant regulatory requirements should be justified, as applicable. The applicant may reference relevant standards.

If applicable, a confirmation that the software was properly qualified to ensure that it performs as intended should be provided.

2.3.4.MD.S Storage

(Medical Device Name) [Manufacturer]

Where relevant, this section may discuss information about the retest period/shelf life for the device. The applicant may define and justify packaging and storage requirements, e.g., to maintain device sterility and integrity during storage and transportation prior to its integration in the medicinal product or for co-packaged device, throughout the medicinal product shelf life.

2.3.4.PM Packaged Medicinal Products for multiconstituent products, if Applicable

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage form] [Strength]

2.3.4.PM.D Description

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

This section should describe the development of the final packaging configuration for medicinal products that are packaged together in a container or in a unit (multiconstituent products), including the justification of this configuration (e.g., suitability for the intended use), as appropriate.

The choice of the additionally packaged device, any other additionally packaged constituents, or referenced device / administration set and their compatibility with drug product and how it reflects on the formulation development should be discussed. Any change in the device design and operating characteristics during the medicinal product development that may impact safety, and/or performance and/or instructions for use of the overall medicinal product may be discussed, explaining the differences, if any, between the study device and its commercial form.

If a transformation of the drug product before administration is necessary, the applicant should include this information in 2.3.4.PH.D.

2.3.4.PM.M Manufacture

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

If the secondary packaging process directly affects product quality, this section should describe the development of the process for packaging of the different constituents into the final container.

2.3.4.PM.C Control

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

This section may include release and stability control strategy development and justification for the packaged medicinal product and packaged constituents (if not included in 2.3.4.DP or 2.3.4.MD).

2.3.4.PM.S Storage

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

2.3.4.PM.S.1 Container closure system

If functional secondary packaging is applied, the rationale for the choice of the packaging material should be discussed.

2.3.4.PM.S.2. Stability, storage conditions, and shelf life

If the storage condition and shelf life differ from those of its individual components, this section should describe the rationale for this difference. As the expiration dates of the individual components may differ, the expiration dating rules of the packaged medicinal product should be provided.

For drug product(s) used with an additionally packaged device or any other additionally packaged constituent (without a necessary transformation before administration), a summary of the stability studies performed, including the conclusion of the studies should be included.

This section may also include a summary and conclusions for shipping studies for the packaged medicinal product.

2.3.4.PH Pharmaceutical Product after transformation, if Applicable

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

2.3.4.PH.D Description

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

This section should discuss the development of the necessary transformation of the drug product and its justification, including any changes during development. The discussion should include the compatibility of the drug product(s) with any constituent(s) as well as diluent(s) including max/min diluting concentrations to provide appropriate and supportive information for the labelling. Additionally, this discussion may include use of alternate administration media (e.g., juice, yogurt) and/or alternate directions of use (e.g., feeding tube).

If a device is used in direct contact with the pharmaceutical product after transformation, the choice of the device and its compatibility with formulation should be discussed.

If applicable, any change in the device design and operating characteristics during the medicinal product development that may impact safety, and/or performance and/or instructions for use of the overall medicinal product may be discussed, explaining the differences, if any, between the study device and its commercial form.

2.3.4.PH.M Manufacture

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

Not applicable.

2.3.4.PH.C Control

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

This section should describe and justify the controls, such as appearance after transformation of drug product and cross-referencing release/stability/shelf-life specifications of the drug product, where relevant. To demonstrate that product quality is maintained during the intended in-use period, the controls should be justified.

2.3.4.PH.S Storage

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

2.3.4.PH.S.1 Stability, storage conditions, and shelf life

The types of studies conducted, protocols used, and the results of the studies should be summarised. This information should cover the recommended in-use storage conditions and in-use period. Similarly, this section may discuss admixture or dilution of products prior to administration, such as product added to large volume infusion containers.

2.3.4.AP Analytical Procedures

(Analytical Procedure Name or code) [Purpose] [Material Type]

This section should include all non-compendial and adjusted analytical procedures used in the control strategy in this section.

2.3.4.AP.1 Analytical Procedure Justification

A discussion of the analytical procedure, explaining the purpose of the procedure, the analytical principles used, and justifying the suitability of the test may be presented.

2.3.4.AP.2 Analytical Procedure Validation/Qualification

This section should summarise the validation/qualification of the analytical procedures. This summary should include the tested performance characteristics, acceptance criteria, and results.

2.3.4.AP.3 Analytical Procedure Development

When development information is necessary, a summary of this information is presented here (ICH Q14 or applicable guidelines).

2.3.5 Product Lifecycle Management

The applicant should use this section to include a change summary and justification for post-approval change submissions (2.3.5.1). The Product Lifecyle Management Document (PLCM, 2.3.4.2) outlines the specific plan for product lifecycle management according to ICH Q12. It includes Established Conditions (ECs), reporting categories for changes to ECs, PACMPs, and/or any post approval CMC commitments in various submission types, including those with or referencing a master file, covering initial marketing authorisation and post-approval changes.

2.3.5.1 Change Summary and Justifications

This section should be provided for each post-approval change application and include the following details:

- A summary of the proposed change and background;
- A table with present and proposed content, including listing of the updated CTD sections with cross-referencing to information in those sections;
- The justification for the proposed update(s) which may be provided directly in this section with a cross-reference to 2.3.3 and Module 3.2, if applicable. Alternatively, justification for the proposed update may cross-reference the updated relevant subsection(s) of 2.3.4.

2.3.5.2 Product Life Cycle Management Document (PLCM)

2.3.5.2.1 List of Established Conditions and Reporting Categories (Optional)

Unless otherwise specified by regional requirement, identifying ECs in CQI for a given product is not mandatory (ICH Q12). If the applicant identifies ECs according to ICH Q12 or ICH Q14, the ECs should be listed in this section, cross-referencing their detailed identification and justification in the relevant subsections of 2.3.4. ECs should be listed in a tabular format or have an unambiguous reference to which part of the information in 2.3.3 CQI is proposed as EC (e.g., for a specification). The applicant may propose ECs for all, or part of the information presented in 2.3.3 CQI. If ECs are proposed for only a part of the information in 2.3.3 CQI, the scope should be clearly defined in this section.

The applicant may specify reporting categories when making a future change to an EC. If the applicant does not propose a reporting category for an EC, the change should follow regional guidelines. A detailed justification for the reporting categories should be included in the relevant subsections of 2.3.4.

2.3.5.2.2 Post-approval Quality Commitments, if Applicable

The applicant should list specified post-approval CMC commitments agreed between the MAH and regulatory authority at the time of approval in tabular format in this section. This may

include, for example, additional data to be submitted post-authorisation, or protocols for studies with or without a regulatory communication. If applicable, the actual descriptions or protocols should be provided in the appropriate 2.3.3 section and referenced here.

The applicant should update this section during the product lifecycle to reflect the current state of open and fulfilled commitments.

2.3.5.2.3 List of Post-Approval Change Management Protocols, if Applicable

The applicant should list PACMPs which they intend to implement in this section.

2.3.5.3 Content of Post-Approval Change Management Protocols, if Applicable

The applicant should include actual protocols in this section. For PACMPs involving multiple medicinal products, a cross-reference can be included as applicable.

When a change is implemented, the applicant should update the relevant information in 2.3.3 via regulatory communication. The applicant may also need to update or amend other sections of Modules 2 and 3.

2.3.6 Product Quality Benefit Risk (Optional)

Product Quality Benefit Risk considerations (PQBR) are expected to support the overall benefit risk discussion in 2.5 Clinical overview (M4E – Efficacy). Cross-references to other sections of the CTD may be included. The assessment of the PQBR is particularly relevant during the initial medicinal product application in some expedited review pathways (e.g., high unmet medical need). In such cases, a summary that explains the applicant's approach or rationale regarding the mitigation of the quality risks should be provided, concluding how the anticipated patient-centric benefits outweigh these residual risks or uncertainties and assessing the impact on safety and/or effectiveness of the product's usage.

Potential risks associated with quality may arise from aspects of product design, manufacturing, and associated overall control strategy, or from uncertainties due to evolving level of knowledge on the product and process available at time of filing (ICH Q9).

Such considerations could address the quality related aspects of the medicinal product in relation to its therapeutic context (e.g., treatment and treatment duration, therapeutic index), and potential benefits (e.g., unmet medical need). An explanation why the product quality is considered adequate should be provided, in view of the intended use of the product, ensuring that the applicable standards are met.

This section may also address difficulties in adopting ICH-recommended approaches, novel strategies, or situations where clinical context significantly influences the quality strategy.

This section may be updated as appropriate to reflect significant changes to the outcome of the PQBR assessment or the residual risks throughout the product lifecycle.

MODULE 3. QUALITY

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.DS Drug Substances

(Drug Substance Name) [Manufacturer]

3.2.DS.D Description

(Drug Substance Name) [Manufacturer]

This section should include information supporting the drug substance structure and general properties such as physicochemical and biological properties.

3.2.DS.M Manufacture

(Drug Substance Name) [Manufacturer]

3.2.DS.M.1 Description of manufacturing process

In support of information provided in 2.3.3, this section should include a suitably detailed description of the commercial manufacturing process, including all steps (i.e., unit operations), critical and other process parameters, and IPCs along with their control ranges/acceptance criteria that are intended to ensure that a drug substance of appropriate quality is consistently produced.

3.2.DS.M.2 Development of manufacturing process and process controls

This section should include process development information and data that support and justify the process parameters and material attributes necessary to ensure drug substance quality. In addition, supporting information and data should be included to identify and confirm the functional relationships of material attributes and process parameters to drug substance CQAs. If applicable, supporting information and data for the basis for the design space, including risk analyses studies linking the manufacturing process to drug substance quality may be included (ICH Q11).

Studies and data of processes models should be included in this section.

Additional information for equipment may be provided in this section.

3.2.DS.M.3 Extractable and leachable studies

Extractables and leachables studies for equipment should be provided in this section, where relevant.

3.2.DS.M.4 Viral clearance studies

This section may include information on viral clearance studies.

3.2.DS.M.5 Changes during development

Relevant data from comparability studies for drug substance manufacturing development and the drug substance proposed commercial manufacturing process should be provided.

3.2.DS.M.6 Comparability for multiple manufacturing sites

In the case of more than one manufacturing site/process, comparative studies should be provided.

3.2.DS.M.7 Process validation or evaluation studies

This section should include relevant data or studies for process evaluation/validation for biologics and aseptic processing/sterilisation for chemical entities demonstrating that the manufacturing process (including any reprocessing) is suitable for its intended purpose and to substantiate selection of process parameters and IPCs.

3.2.DS.C Control

(Drug Substance Name) [Manufacturer]

3.2.DS.C.1 Batch analysis

This section should include the results of batch analysis or CoAs for relevant batches (for example stability, nonclinical, and clinical).

3.2.DS.C.2 Justification of specifications

Any relevant supportive information and studies/data justifying specification(s) may be provided here.

3.2.DS.S Storage

(Drug Substance Name) [Manufacturer]

3.2.DS.S.1 Container closure system

Relevant documents for the container closure system which may include extractables and leachables data/studies should be provided, where appropriate, as well as data from studies conducted to select and demonstrate the suitability of the container closure systems.

Relevant batch analysis or CoA(s) for container closure system(s) should be provided, as appropriate.

3.2.DS.S.2 Stability, storage conditions, and retest period/shelf life

This section should include relevant information/data in support of justifying storage conditions and retest period or shelf life of the drug substance. If applicable, relevant information/data in support of handling and shipping of the drug substance should be provided.

3.2.SI Substance Intermediates, if Applicable

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

This section should include a cross-reference to information in 3.2.DS.M highlighting the steps that produce substance intermediates.

3.2.SI.D Description

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

If applicable, information on the description of the substance intermediate should be included.

3.2.SI.M Manufacture

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

If applicable, this section may include supportive studies of the manufacture of substance intermediate. In this case, the applicant should follow all recommendations stated under 3.2.DS.M.

3.2.SI.C Control

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

Batch analysis results should be provided to support the specifications of the substance intermediates, as appropriate.

3.2.SI.S Storage

(Substance Intermediate Name) [Manufacturer] [Drug Substance Name]

3.2.SI.S.1 Container closure system

Data from studies conducted to select and demonstrate the suitability of the container closure system and extractables and leachables data/studies should be included, where relevant. Relevant batch analysis or CoA(s) for container closure system(s) should be provided, as appropriate.

3.2.SI.S.2 Stability, storage conditions, and retest period/shelf life

If applicable, this section should include stability data supporting the storage conditions and the proposed retest period/shelf life, and shipping conditions of the substance intermediates (ICH Q1/Q5C).

3.2.SM Starting/Source Materials

(Starting Material Name) [Drug Substance Name]

3.2.SM.D Description

(Starting Material Name) [Drug Substance Name]

Additional information on the description of starting/source materials may be provided, as appropriate.

3.2.SM.M Manufacture

(Starting Material Name) [Drug Substance Name]

Additional information on manufacture of starting/source materials may be provided, as appropriate.

3.2.SM.C Control

(Starting Material Name) [Drug Substance Name]

Where appropriate, this section should include the batch analysis data or CoAs. For biological starting materials, additional characterisation and adventitious agent control information may be provided (ICH Q5A, Q5B, Q5D, Q11). The applicant should discuss control of adventitious agents in 2.3.4.IN.2.2, if applicable (ICH Q5A).

3.2.SM.S Storage

(Starting Material Name) [Drug Substance Name]

For biological starting materials, additional information on the shipping/stability of the starting/source material may be provided.

3.2.RM Raw Materials

(Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance Manufacturer]

3.2.RM.D Description

(Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance Manufacturer]

This section may include additional information on the description of the raw material.

3.2.RM.M Manufacture

(Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance Manufacturer]

Additional manufacturing information (e.g., information on manufacture relevant to adventitious agent control for biological raw materials) may be provided (ICH Q5A).

3.2.RM.C Control

(Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance Manufacturer]

If applicable, this section should include batch analysis data or CoA. For biological raw materials, additional information regarding adventitious agent control may be provided. The applicant should discuss control of adventitious agents in 2.3.4.IN.2.2, if applicable (ICH Q5A).

3.2.RM.S Storage

(Raw Material Name) [Drug Substance Name] [Manufacturer] [Intermediate Substance Manufacturer]

For biological raw materials, this section may include supportive stability information/data.

3.2.EX Excipients

(Excipient Name) [Drug Product Name] [Manufacturer]

Where appropriate (e.g., for novel excipients and adjuvants), applicable supportive data regarding description, manufacture, control, and storage may be provided in respective 3.2.EX sections.

For compendial excipients, these sections will typically be limited to information that justifies the adequacy of the proposed excipient specifications (e.g., through batch analysis data).

3.2.EX.D Description

(Excipient Name) [Drug Product Name] [Manufacturer]

Supportive information/data may be provided on the description, as appropriate.

3.2.EX.M Manufacture

(Excipient Name) [Drug Product Name] [Manufacturer]

This section may include information/data on the manufacturing process and process control, as appropriate.

3.2.EX.C Control

(Excipient Name) [Drug Product Name] [Manufacturer]

Batch analysis data may be provided, as appropriate. For biological excipients, additional information about control of adventitious agents, may be provided, as appropriate (ICH Q5A).

3.2.EX.S Storage

(Excipient Name) [Drug Product Name] [Manufacturer]

Information/data in support of the claimed storage conditions and retest period/shelf life may be provided, as appropriate.

3.2.RS Reference Standards and/or Materials

(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]

3.2.RS.D Description

(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]

This section may include additional information on the description of reference standards and/or materials.

3.2.RS.M Manufacture

(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]

Additional information on the manufacture of in-house reference materials may be provided.

3.2.RS.C Control

(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]

For in-house reference materials, batch analysis data should be provided. For biological in-house reference materials, additional supportive information on characterisation, and calibration or qualification may be included.

3.2.RS.S Storage

(Reference Standard Name) [Manufacturer] [Drug Substance Name] [Drug Product Name]

For biological in-house reference materials, stability information/data to support the claimed use period and storage conditions may be provided.

3.2.IM Impurities

3.2.IM.D Description

For impurities (chemical impurities, degradants, product- and process-related impurities) reported in the specifications of drug substance and/or drug product, this section should include basic information on the impurity such as nomenclature, structural formula, and type/origin. Information supporting the identification, characterisation, verification, or qualification of the impurity may also be provided, when appropriate (ICH Q3A, Q3B, Q3C, Q3D, Q3E, Q6A/Q6B, M7).

For impurities not reported in the specifications, the same basic information may be provided, as appropriate.

3.2.IM.M Manufacture

Not applicable.

3.2.IM.C Control

Not applicable.

3.2.IM.S Storage

Not applicable.

3.2.DP Drug Products

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

3.2.DP.D Description

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

3.2.DP.D.1 Components of the drug product

This section should include information from experimental designs used in identifying critical or interacting variables that might be important to ensure the quality of the drug product. Studies that demonstrate the compatibility of drug substance(s) and excipients with each other and with integral devices, along with information supporting introduction of a device, may also be included.

3.2.DP.D.2 Formulation development

This section should include information and results of the studies and/or published literature that were used to support the proposed dosage form, formulation development, and to justify the proposed excipients ranges. For complex dosage forms, additional details or diagrams may be provided to enhance understanding of the formulation.

3.2.DP.D.3 Comparability during formulation and product development

Information on comparative *in vitro* studies (e.g., dissolution) may be included, as appropriate.

Information supporting changes in the device during product development may also be included.

3.2.DP.D.4 Physicochemical and biological properties of drug product

Any supportive information may be provided.

3.2.DP.D.5 Microbiological attributes

Any supportive information may be provided.

3.2.DP.M Manufacture

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

3.2.DP.M.1 Description of manufacturing process

In support of information provided in 2.3.3, the applicant should include a suitably detailed description of the commercial manufacturing process including all steps (i.e., unit operations), critical and other process parameters and IPCs with their control ranges/acceptance criteria that are intended to ensure that a drug product of appropriate quality is consistently produced.

3.2.DP.M.2 Development of manufacturing process and process controls

This section should include data and results from specific development studies and/or published literature that support the manufacturing process development. Novel processes or technologies and packaging operations should be described.

Information from process and product monitoring conducted throughout development that is used to justify and establish the control strategy for manufacturing should be provided. Additionally, studies and experiments that support manufacturing process development and monitoring programs, including the risk assessment studies may be provided (ICH Q8, Q9).

This section may include information that provides the basis for the design space(s). This may include risk analyses studies and functional relationships linking material attributes and process parameters to product CQAs, and risk analyses studies linking the design of the manufacturing process to product quality.

Additional information about equipment may be provided in this section.

Studies and data of processes models should be included in this section.

3.2.DP.M.3 Extractable and leachable studies

Extractables and leachables studies for equipment should be provided in this section, where relevant.

3.2.DP.M.4 Changes during manufacturing process development

This section should include comparative studies of significant differences between the manufacturing processes used to produce batches for registration/pivotal clinical trials (e.g., safety, efficacy, bioavailability, bioequivalence) or primary stability studies and the proposed commercial processes, if applicable.

3.2.DP.M.5 Comparability for multiple manufacturing sites

In the case of more than one proposed commercial manufacturing site, comparative information should be provided.

3.2.DP.M.6 Process validation or evaluation studies

Relevant documentation and results of the process validation and/or evaluation should be provided, as appropriate. If applicable, this section should include any studies that support proposals for material reprocessing, including studies that demonstrate consistency between reprocessed lots and normal production lots.

3.2.DP.C Control

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

3.2.DP.C.1 Batch analysis

This section should include the results of batch analysis or CoAs for relevant batches (e.g., stability, nonclinical, and clinical).

3.2.DP.C.2 Justification of specifications

Any additional information justifying specification(s) may be provided.

3.2.DP.S Storage

(Drug Product Name) [Manufacturer] [Manufactured Dosage Form] [Strength]

3.2.DP.S.1 Container closure system

Information about container closure system should be provided which may include extractables and leachables studies, where relevant, as well as results from studies conducted to select and demonstrate the suitability of the container closure system. Relevant results of batch analysis or CoA(s) for container closure system(s) should be provided, as appropriate.

3.2.DP.S.2 Stability, storage conditions, and shelf life

This section should include relevant stability results to support storage conditions, shelf life, and/or holding time for each of the proposed container closure system(s).

Relevant studies/results in support of handling and shipping of the bulk product and drug product may be provided.

Additional information may be provided to support in-use storage conditions and in-use period for drug product.

3.2.PI Product Intermediates, if Applicable

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

3.2.PI.D Description

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

This section may include data and information that support the composition and development of the product intermediate.

3.2.PI.M Manufacture

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

Supportive studies of the manufacture of product intermediate may be included, in accordance with recommendations stated under 3.2.DP.M.

3.2.PI.C Control

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

This section should include the results of batch analysis or CoAs to support the specifications for product intermediate, as appropriate.

3.2.PI.S Storage

(Product Intermediate Name) [Manufacturer] [Drug Product Name]

3.2.PI.S.1 Container Closure System

Information for container closure system should be provided which may include results of extractables and leachables studies, where relevant, as well as results from studies conducted to select and demonstrate the suitability of the container closure system. Relevant results of batch analysis or CoA(s) for container closure system(s) should be provided, as appropriate.

3.2.PI.S.2 Stability, storage conditions, holding time, and shelf life

This section should include relevant stability results in support of justifying storage conditions, holding time/shelf life of product intermediate(s).

Relevant studies/results that support the proposed handling and shipping conditions for the

product intermediate may be provided.

3.2.MD Medical Devices, if Applicable

(Medical Device Name)

3.2.MD.D Description

(Medical Device Name) [Manufacturer]

If applicable, this section should include detailed information on the device. This may include a comprehensive description of the device and its components.

3.2.MD.M Manufacture

(Medical Device Name) [Manufacturer]

If applicable, detailed information relating to the manufacture of the device should be provided. This may include a detailed description of the manufacturing process, information related to the manufacturing process development and commercial manufacturing process, including the sterilisation step (if applicable), and results of the process validation for critical steps in the device manufacturing process.

3.2.MD.C Control

(Medical Device Name) [Manufacturer]

If applicable, this section should include detailed information relating to the control of the device. This may include information related to the control strategy and/or batch analysis data.

If applicable, validation testing data that confirms that the device meets specified requirements may be submitted.

3.2.MD.S Storage

(Medical Device Name) [Manufacturer]

If applicable, this section should include detailed information relating to the storage of the device before its integration in the medicinal product or for co-packaged device throughout the medicinal product retest period/shelf life.

3.2.PM Packaged Medicinal Products for multiconstituent products, if Applicable

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

3.2.PM.D Description

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

This section should include information supporting introduction of a device or changes in the device during medicinal product development may also be provided.

3.2.PM.M Manufacture

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

If the packaging process directly affects product quality, information regarding the process for packaging of the additionally packaged constituents into the final container should be provided, as appropriate.

3.2.PM.C Control

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

This section may include analytical results and information for the proposed packaged

medicinal product control strategy.

3.2.PM.S Storage

(Packaged Medicinal Product Name) [Manufacturer] [Combined Dosage Form] [Strength]

3.2.PM.S.1 Container closure system

If functional secondary packaging material is applied to the packaged medicinal product, supportive information should be provided.

3.2.PM.S.2 Stability, storage conditions and shelf life

This section may include relevant information to support justification of in-use storage conditions and in-use period, shipping conditions, as well as storage conditions and shelf life of the packaged medicinal product.

3.2.PH Pharmaceutical Product after transformation, if Applicable

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

3.2.PH.D Description

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

Supporting information should be provided, including compatibility tests. Information supporting introduction of a device or changes in the device during medicinal product development may also be included.

3.2.PH.M Manufacture

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

Not applicable.

3.2.PH.C Control

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

This section should include information to ensure product quality during the intended in-use period.

3.2.PH.S Storage

(Pharmaceutical Product Name) [Manufacturer] [Administrable Dosage Form] [Strength]

3.2.PH.S.1 Stability, storage conditions, and shelf life

Relevant information to support justification of in-use storage conditions and in-use period of the pharmaceutical product after transformation should be provided.

3.2.AP Analytical Procedures

(Analytical Procedure Name or code) [Purpose] [Material Type]

This section may include all non-compendial analytical procedures, that are used throughout the application, not only the procedures used in support of the control strategy. This section may also include analytical procedures including dissolution methods that are used throughout the development and comparative studies, but not directly used in the control strategy.

3.2.AP.1 Analytical Procedure Description

For analytical procedures already described under 2.3.3.AP, a more detailed description may

be included in this section.

Analytical procedures not described under 2.3.3.AP, and that are referenced in the dossier, should be presented here. The level of detail should be appropriate for the intended use.

3.2.AP.2 Analytical Procedure Validation/Qualification

Where validation is recommended according to ICH Q2, this section should include detailed data. This may also include verification or method transfer data, where appropriate. Information on analytical procedures requiring ongoing monitoring and/or periodic (re)calibration (e.g., model for multivariate analytical procedures) should also be provided in this section.

3.2.AP.3 Analytical Procedure Development

When development information is recommended, related data and information should be included in this section (ICH Q14 or applicable guidelines).

3.2.FA Facilities

[Manufacturer]

The applicant should adhere to regional guidelines for their specific submission and product. For biologics, this section should include the facilities and equipment information listed below. Regulatory authorities may have different pathways for facility information gathering, such a Site Master File or GMP certificate from the inspectorate and therefore, may not need the facility information listed here; whereas other authorities may require additional or less information than what is listed below.

1. A diagram of the manufacturing facility including:
    - the manufacturing activities taking place in each room;
    - the manufacturing flow (including movement of materials, personnel, waste, and intermediate(s)) in and out of the manufacturing areas;
    - the classification for each room.
2. Information on the type/classes (e.g., antibody, cytokine, insulin, high-potency drugs) of all developmental or approved products manufactured or manipulated in the same areas as the applicant's product, along with the cell line used for each product (e.g., *E. coli*, CHO).
3. A summary description of product-contact equipment, and its use (i.e., dedicated or shared use, manufacturing step(s) where it is used).
4. The cleaning strategy, e.g., shared use equipment, change-over process, demonstration of adequacy of cleaning.
5. A summary of the environmental monitoring program in aseptic manufacturing area.
6. Information on sterilisation of specified equipment and product components.

In addition, the applicant may be able to refer to a previously submitted application for the same facility.

ABREVIATIONS

AP - Analytical Procedure

ATMP - Advanced Therapy Medicinal Products

CoA - Certificate of AnalysisCQA - Critical Quality Attributes

CQI - Core Quality Information

DMCS - Description, Manufacture, Control, and Storage

DP - Drug Product

DS - Drug Substance

ECs - Established Conditions

EX - Excipient

FA – Facilities

IN - Integrated Development and Justification

IPC - In Process Control

MD - Medical Device

OCS - Overall Control Strategy

PM - Packaged Medicinal Product

PACMP - Post Approval Change Management Protocol

PH – Pharmaceutical Product

PLCM - Product Lifecycle Management

PQBR - Product Quality Benefit Risk

PI - (Drug) Product Intermediate

QTPP - Quality Target Product Profile

RM - Raw Material

RS - Reference Standard

RTRT - Real Time Release Testing

SI - (Drug) Substance Intermediate

SM - Starting/Source Material

GLOSSARY

Term(s)	Definition	Reference/Related Terms
Analytical procedure	The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.	ICH Q2
Bioinformatics	Bioinformatics is an interdisciplinary field that combines biology, computer science, mathematics, and statistics to analyse and interpret biological data. It involves the use of computational tools and techniques to manage, process, and understand complex biological information, particularly large datasets generated by experiments such as DNA sequencing, protein structure analysis, and gene expression studies.	
Bulk Material (Biologics)	The material which is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients including other components such as buffers.	ICH Q6B
Bulk Product	Bulk finished dosage form, that has completed all processing stages before immediate packaging *Note 1: This includes materials that may be held in potentially large quantities for an extended period of time under controlled and justified conditions (e.g. 10 000 tablets intended for blistering or 100L of solution for injection intended to fill vials)* *Example: film-coated tablet or solution for injection before immediate packaging*	M4Q(R2) adapted from ICH Q6B/Bulk Material
(Chemical) Development Studies	Studies conducted to scale-up, optimise, and validate the manufacturing process for a new drug substance or a drug product.	ICH Q3A/B
Container Closure System	The sum of packaging components that together contain and protect the finished dosage form or any other material. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional	ICH M4Q(R2) adapted from ICH Q1A

Term(s)	Definition	Reference/Related Terms
	protection to the drug product or packaged material.	
Contamination	The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or drug substance during production, sampling, packaging or repackaging, storage or transport.	ICH Q7
Control Strategy	A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.	ICH Q10
Dosage Form	The type of physical manifestation (e.g., tablet, capsule, solution, cream, powder).	ICH M4Q(R2) Adapted from ISO IDMP
Drug Product	The Finished Dosage Form in the final immediate packaging intended for sale or supply. *Note: Some Drug Products do not necessarily include a Drug Substance (e.g. solvent for solution for injection in vial)* *Note: Label is not included* *Examples: film-coated tablet in blister or solution for injection in vial, solvent for solution for injection in vial*	ICH M4Q(R2)
Drug Release Profile	Speed/rate at which a drug is released.	
Drug Substance	Any substance or mixture of substances intended to be used in the manufacture of a finished dosage form and that, when so used, becomes an active ingredient of that finished dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.	ICH M4Q(R2) Adapted from ICH Q7/ Active Substance/ Active Ingredient
Excipient	–A substance or compound, other than the drug substance and packaging materials,	ICH M4Q(R2)

Term(s)	Definition	Reference/Related Terms
	that is intended or designated to be used in the manufacture of a finished dosage form. *Note: Excipients include e.g. fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances, processing aids etc., as well as the constituents of the outer covering of the finished dosage form, e.g. gelatine capsules.*	
Finished Dosage Form	Final qualitative and quantitative composition containing one or more ingredients in the specific manufactured dosage form intended to be part of a drug product *Note: Some Finished Dosage Form do not necessarily include a Drug Substance (e.g. solvent for solution for injection)* *Example: film coated tablet or solution for injection with specific qualitative and quantitative composition*	ICH M4Q(R2)/ *Manufactured Item (ISO IDMP 11615)*
Functional secondary packaging material	Secondary packaging material considered critical to ensure the quality of the packaged substance/ product *Example: provides additional protection like for moisture sensitive products or serves to deliver the product*	ICH M4Q(R2) adapted from ICH
Impurity	(1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance. (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product. (3) Any component present in the drug substance or drug product which is not the desired product, a product-related substance, or excipient including buffer components. It may be either process- or product-related.	ICH Q6A/B/ Degradation product
Material	A general term used to denote raw materials, starting materials, substance intermediates, drug substances, excipients, reference standards, product intermediates, finished dosage forms, and packaging and labelling materials.	ICH M4Q(R2) Adapted from ICH Q7
Medicinal Product	Pharmaceutical product or combination of pharmaceutical products that can be administered to human beings or animals for treating or preventing disease, with the aim of making a medical diagnosis or to restore, correct or modify physiological functions	ISO IDMP 11615

Term(s)	Definition	Reference/Related Terms
	Note 1: A medicinal product may contain in the packaging one or more finished dosage form(s), and one or more pharmaceutical products. *Note 2: In certain regions, a medicinal product is defined as any substance or combination of substances that can be used to make a medical diagnosis.*	
Multiconstituent Product(s)	Multiconstituent products consist of two or more constituents that are intended to be used together for a specific therapeutic, diagnostic or preventive purpose, and that are packaged in a container or in a unit as a marketing pack. Multiconstituent products may include one or more drug product constituents, or a combination of these with additional finished dosage forms and/or medical device(s). *Examples: a vial containing powder for solution for injection may be packaged with a vial containing the vehicle for preparation of solution for reconstitution, along with two syringes: one for preparation of the solution for injection and the other for administration of the solution for injection*	ICH M4Q(R2)
Packaging Material	Any material intended to protect another material during storage and transport.	ICH M4Q(R2) adapted from ICH Q7
Packaged Medicinal Product	Medicinal Product in a container being part of a package, representing the entirety that has been packaged for sale or supply *Note: Packaged Medicinal Product may contain Multiconstituent Product* *Examples: film-coated tablet in blister in carton box or solution for injection in vial in carton box or one vial with powder for solution for injection is packaged with one vial with the vehicle for preparation of solution for reconstitution and with two syringes for preparation of the solution for injection and for administration of the solution for injection in a carton box*	ISO IDMP/ Marketing Pack
Pharmaceutical Product	Qualitative and quantitative composition of the product as administered to the patient in line with regulated product information. *Note 1: In many instances, the pharmaceutical product is equal to the finished dosage form. However, there are instances where the finished dosage form must undergo a transformation before being administered to the patient (as the pharmaceutical product) and the two are not equal.* *Examples: film-coated tablet (taken without transformation) or reconstituted solution for injection using one vial with powder for solution for injection is packaged with one vial with the vehicle for preparation of solution for reconstitution.*	ISO IDMP

Term(s)	Definition	Reference/Related Terms
(Drug) Product Intermediate	A material that is produced as part of the drug product manufacturing process after the defined drug substance(s) and subject to further processing before the finished dosage form. *Note 1: Generally, a product intermediate will have established specifications to determine the successful completion of its manufacture before the continuation of the drug product manufacturing process.* *Note 2: This includes materials that may be held for an extended period of time under controlled and justified conditions or tested against the established specification immediately prior to further processing.* *Note 3: A product intermediate may be produced by the final drug product manufacturer or manufactured or sourced via an independent manufacturing process by a different manufacturer* *Note 4: A product intermediate may not contain the drug substance such as excipient mixtures, granulated excipients, tablet core without drug substance, placebo intermediates.*	ICH M4Q(R2) Adapted from ICH Q5C/ Pharmaceutical intermediate
Quality	The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as identity, strength, and purity. The degree to which a set of inherent properties of a product, system or process fulfils requirements.	ICH Q6A ICH Q9
Raw Material	A general term used to denote reagents, solvents and processing aids intended for use in the production of substance intermediate(s) or drug substance(s) and not being the defined starting material(s).	Adapted from ICH Q7
Reference Standard	Primary - A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material. Secondary - A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.	ICH Q7/ Reference Standard In-house Primary Reference Material Reference standards and/or material Specified substance ICH Q7/Reference

Term(s)	Definition	Reference/Related Terms
		Standard In-house Working Reference Material Secondary Reference Standard Specified Substance
(Drug) Substance Intermediate	A material that is produced as part of the end-to-end drug substance manufacturing process after the defined starting material(s) and subject to further processing before the drug substance. *Note 1: Substance intermediates may or may not be isolated.* *Note 2: Generally, a substance intermediate will have established specifications or in-process controls to determine the successful completion of its manufacture before the continuation of the drug substance manufacturing process.* *Note 3: This includes materials that may be held for an extended period of time under controlled and justified conditions or tested against the established specification immediately prior to further processing* *Note 4: A substance intermediate can be produced in-house by the main drug substance manufacturer or manufactured or sourced via a separate manufacturing process or by a different manufacturer* *Note 5: In some cases, the active substance might be considered as a substance intermediate of the final drug substance (e.g. diclofenac free base is a substance intermediate of the diclofenac sodium drug substance)* *Note 6: For very complex end to end biologic drug substance manufacturing processes or cases where the sub-part of the end-to-end drug substance manufacturing process up to a specific substance intermediate is performed by a different manufacturer, the applicant may segregate the manufacture of specific substance intermediates (e.g. viral vectors, ADC linker etc.) from the main drug substance manufacturing process.* *Note 7: The level of quality information expected for a substance intermediate will depend on its complexity and on the potential impact of the quality of this material to the quality of the final drug substance; with higher level risk materials (e.g. viral vectors, ADC linkers, etc.) requiring a level of information close to a drug substance.* *Examples: an isolated or non-isolated substance intermediate manufactured as part of the main drug substance manufacturing process, or a chemical or a biological substance manufactured outside of the main drug substance manufacturing process (a linker used in ADC manufacture, a viral vector used in*	ICH M4Q(R2) Adapted from ICH Q5C

Term(s)	Definition	Reference/Related Terms
	cell and gene therapy manufacture etc.). *Further processing examples: further chemical transformation, further molecular change/modification, purification*	
Starting/Source Material	A material from which the drug substance is extracted or used in the production of a drug substance and ultimately incorporated as an element into the structure of the drug substance (directly or via one of its substance intermediate). *Note 1: Starting material can be commercially available, produced in-house by the final drug substance manufacturer or externally by one or more different manufacturers under contract or commercial agreement.* *Note 2: Starting materials are normally of defined chemical properties and structure.*	ICH M4Q(R2) Adapted from ICH Q3A(R2)
Specification	A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.	ICH Q6A/B
Substance	Matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical.	ISO IDMP
Transformation	Procedure that is carried out in order to convert a finished dosage form that requires such a modification into a pharmaceutical product, i.e. from its manufactured dosage form to its administrable dosage form *Note 1: A transformation is not required when the drug product dosage form is equal to the pharmaceutical product.* *Note 2: In certain circumstances, the transformation may be used, alone or in combination with one or more other pharmaceutical dosage form attributes, to describe a medicinal product where a pharmaceutical dosage form term cannot be used, for example as part of an adverse event report in which the precise pharmaceutical dosage form is unknown, but the transformation is known.*	ICH M4Q(R2) Adapted from ISO IDMP 11615

Term(s)	Definition	Reference/Related Terms
	Note 3: The transformation should be applied within context of product quality and M4Q (R2) guideline and should not be interpreted in a biological sense, such as genetic cellular alterations or change from normal to malignant cells etc. *Examples: Dilution, dissolution, dispersion, suspension, reconstitution.*	

1639
1640

REFERENCES

ICH M7(R2): Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

ICH Q1: Stability Series (Q1A-Q1F)

ICH Q2: Validation of Analytical Procedures: Text and Methodology

ICH Q3: Impurity Series (Q3A-Q3E)

ICH Q5A(R2): Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin

ICH Q5B: Quality Of Biotechnological Products: Analysis of the Expression Construct in Cells Used For Production of R-DNA Derived Protein Products

ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products

ICH Q5D: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products

ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

ICH Q8: Pharmaceutical Development

ICH Q9: Quality Risk Management

ICH Q10: Pharmaceutical Quality System

ICH Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

ICH Q11 Q&A: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Questions and Answers

ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products

ICH Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation