

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
USE

DRAFT CONSENSUS GUIDELINE

**THE COMMON TECHNICAL DOCUMENT FOR THE
REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE**

QUALITY

Released for Consultation
at *Step 2* of the ICH Process
on 20 July 2000
by the ICH Steering Committee

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 Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

THE COMMON TECHNICAL DOCUMENT

QUALITY

Draft ICH Consensus Guideline

Released for Consultation, 20 July 2000, at *Step 2* of the ICH Process

QUALITY OVERALL SUMMARY (QOS)

The Quality Overall Summary (QOS) is a summary which follows the outline of the core dossier (Module III). The QOS cannot include information, data or justification that was not already included in the body of the Quality Module III or in other parts of the CTD (e.g. CTD-E, CTD-S).

The QOS should include sufficient information from each section to provide the Quality reviewer with an overview of the Quality Module III. The QOS should also emphasise critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of salient and critical issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S module).

This QOS normally should not exceed 40 pages of text excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text excluding tables and figures.

The QOS should follow the outline of the core dossier (Module III) and include the basic information described below:

INTRODUCTION

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

S DRUG SUBSTANCE

S1 General Information

Information as provided in S1.

S2 Manufacture

Information as provided in S2.

Information on the manufacturer. A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality.

A flow diagram as provided in S2.2.

Additionally for Biotech:

A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in S2.3.

A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Identification of critical process intermediates including specifications and storage conditions, as described in S2.4.

A description of process validation or evaluation as described in S2.5

A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in S2.6. The QOS should also cross-refer to the nonclinical and clinical studies which used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

S3 Characterisation

For NCE

A summary of the interpretation of evidence of structure and isomerism, as described in S3.1.

When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance which is to be used in the final product intended for marketing.

For Biotech:

A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure, and biological activity) as described in S3.1.

For NCE and Biotech:

The QOS should summarise the data on actual and potential impurities (for biotech: product-related and process-related impurities) arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also discuss the comparative analysis of the impurity levels in batches of the drug substance used in the nonclinical studies, in the clinical trials and in typical batches manufactured by the proposed commercial process to examine whether the impurity levels have changed, and how the specified impurity limits relate to the levels found. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary and/or a graphical representation of the data provided in S3.2 (for NCE only, see Q3A).

S4 Control of Drug Substance

A brief summary of the justification of the specification(s), and the analytical validation.

Specification as provided under S4.1.

A tabulated summary and/or a graphical representation of the batch analyses provided under S4.4.

S5 Reference Standards or Materials

Information as provided in S5.

S6 Container Closure System

A brief description and discussion of the information, as included in S6.

S7 Stability

A brief discussion of the results and conclusions of the stability studies of batches of drug substance, the proposed storage conditions, and the expiry date or duration of storage before re-testing to check compliance with the specification, as described in S7.1.

A tabulated summary and/or a graphical representation of the stability results as provided under S7.3.

P DRUG PRODUCT

P1 Description and Composition of the Drug Product

Description of the dosage form.

Composition of the drug product and function of the excipients, as described in P1.

Composition as provided under P1.

P2 Pharmaceutical Development

A brief discussion of the information and data presented as in P2.

P3 Manufacture

Information as provided in P3.

Information on the manufacturer. A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.

A flow diagram as provided under P3.3.

P4 Control of Excipients

A brief summary on the quality of excipients as described in P4.

P5 Control of Drug Product

A brief summary of the justification of the specification(s), and a summary of the analytical validation should be provided.

Specification(s) as provided under P5.1.

A tabulated summary and/or a graphical representation of the batch analyses provided under P5.4.

P6 Container Closure System

A brief description and discussion of the information in P6.

P7 Stability

A brief discussion of the results and conclusions of the stability studies and analysis of data. Conclusions with respect to storage conditions and expiry period, and, if applicable, in-use storage conditions and expiry period should be given.

A tabulated summary and/or a graphical representation of the stability results as provided under P7.3.

A APPENDICES FOR BIOTECH

A1 Biotech facilities and equipment

A summary of facility information described under A1.

A2 Viral Safety Evaluation

A discussion on the control and elimination of endogenous and adventitious agents in production (e.g. cell bank, raw materials, manufacturing process).

A tabulated summary of the reduction factors for viral clearance, provided under A2.

THE COMMON TECHNICAL DOCUMENT QUALITY

TABLE OF CONTENTS

Scope	1
Table of Contents	
Drug Substance.....	2
Drug Product	6
Regional Information.....	10
Appendices.....	10

THE COMMON TECHNICAL DOCUMENT

QUALITY

SCOPE

This document is intended to provide guidance on the format of a registration dossier for drug substances and their corresponding drug products as defined in the scope of the ICH Guidelines Q 6 A ("NCE") and ICH Guideline Q 6 B ("Biotech"). This format may also be appropriate for certain other categories of products; to determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities.

Notes:

1. The text following the section titles is intended to be explanatory and illustrative only. It is not all-inclusive and additional regional requirements may apply.
2. In "Part R: Regional Information" all relevant section titles may not be included. Additional "Part R: Regional Information" or section titles may be required by the regional authorities.
3. Neither the type nor extent of specific supporting data have been addressed in this document and may depend upon regional requirements.

Part	Data Module	Reference
S	DRUG SUBSTANCE	
S 1	GENERAL INFORMATION	
S 1.1	<p>Nomenclature</p> <p>Recommended INN, compendial name if relevant, chemical name(s), company or laboratory code, other non-proprietary name(s), e.g., national name, BAN, USAN, JAN; and the Chemical Abstracts Service (CAS) registry number</p>	---
S 1.2	<p>Structure</p> <p>NCE: The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass.</p> <p>Biotech: Schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass as appropriate.</p>	---
S 1.3	<p>General Properties</p> <p>List of physicochemical and other relevant properties of the drug substance, including: biological activity for Biotech.</p>	Q6A, Q6B
S 2	MANUFACTURE	
S 2.1	<p>Manufacturer(s)</p> <p>Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacture and testing.</p>	---
S 2.2	<p>Description of Manufacturing Process and Process Controls</p> <p>The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of drug substances. The following information should be provided to adequately describe the manufacturing process and process controls:</p> <p>NCE:</p> <p>A schematic flow diagram of the synthetic process(es) that includes molecular formulae, weights, and yields; chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry; and identifies operating conditions and solvents.</p> <p>A sequential procedural narrative of the manufacturing process that provides quantities of raw materials, solvents, catalysts and reagents reflecting representative batch scale for commercial manufacture, identifies critical steps, and includes process controls, equipment and operating conditions, such as temperature, pressure, pH, time, etc.</p> <p>Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in S2.5.</p> <p>Biotech:</p> <p>Information on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.</p> <p>Batch(es) and scale definition</p>	Q5A, Q5B, Q6B

Part	Data Module	Reference
	<p>An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale.</p> <p>Cell culture and harvest</p> <p>A flow diagram, which illustrates the manufacturing route from the original inoculum (e.g. cells contained in one or more ampoule(s) of the WCB) up to the last harvesting operation, including all steps and intermediates. Include relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, and temperature. Identify critical steps and intermediates, for which specifications are established (as mentioned in S2.4).</p> <p>The description of each process step mentioned in the flow diagram. Include information on scale; culture media and other additives (details provided in S2.3); major equipment (details provided in A1); process controls including in-process tests and operational parameters for process steps, equipment and intermediates; and acceptance criteria (details provided in S2.4). Information regarding procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage. (Details in S2.4 regarding shipping and storage.)</p> <p>Purification and modification reactions</p> <p>The flow diagram, illustrating the purification steps from the crude harvest(s) up to the step preceding filling of the drug substance. Include all steps and intermediates and relevant information for each stage, such as volumes, pH, critical processing time, and temperatures. Critical steps, for which specifications are established as mentioned in S2.4. The description of each process step (as identified in the flow diagram) with information on scale, buffer and other reagents (details provided in S2.3), major equipment and materials. For materials, such as membranes and chromatography resins, information for conditions of use and reuse. (Equipment details in A1; validation studies for the reuse and regeneration of columns and membranes in S2.5.) The description includes process controls (including in-process tests and operational parameters) acceptance criteria for process steps, equipment and intermediates. (Details in S2.4.)</p> <p>Describe reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance. (Details should be given in S2.5.)</p> <p>Description of procedures used to transfer material from one step to another, from different equipment, areas or buildings, storage and shipping, as appropriate. (Details in S2.4 and A1.)</p> <p>Filling, storage and transportation (shipping)</p> <p>A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria. (Details in S2.4.) The container closure system(s) used for storage of the drug substance. (Details in S 6.) Storage and shipping conditions for the drug substance.</p>	
S 2.3	<p>Control of Materials</p> <p>Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drug substance indicating where each material is used in the process. Tests and acceptance criteria.</p>	Q6A

Part	Data Module	Reference
	<p>Control of Raw Materials and Reagents</p> <p>Information on the quality and control of raw materials and reagents used in the manufacturing process.</p> <p>Raw materials and reagents, including biologically-sourced materials, are used throughout manufacturing (e.g., media components, monoclonal antibodies, enzymes). Information necessary to demonstrate that raw materials meet standards appropriate for their intended use, including the clearance or control of adventitious agents. For biologically-sourced materials this may include detailed information regarding the source, manufacture (e.g., preparation, validation of monoclonal antibody production), characterisation and control</p> <p>Biotech:</p> <p>Control of Source and Starting Materials of Biological Origin</p> <p>Summaries of viral safety information for biologically-sourced materials (Details in A2.)</p> <p>Source, history, and generation of the cell substrate</p> <p>Information on the source of the cell substrate and analysis of the expression construct for recombinant cells and initial cell clone used to develop the Master Cell Bank, as described in Q5B and Q5D.</p> <p>Cell banking system, characterisation, and testing</p> <p>Information on the cell banking system; quality control activities, and cell line stability during production and storage, including procedures used to generate the master and working cell bank(s), as described in Q5B and Q5D.</p>	<p>Q5A, Q5B, Q5C, Q5D, Q6B</p>
<p>S 2.4</p>	<p>Controls of Critical Steps and Intermediates</p> <p>Critical Steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to assure that the process is controlled.</p> <p>Intermediates: Specifications and analytical procedures, if any, for intermediates isolated during the process.</p> <p>Additionally for Biotech: Stability data supporting storage conditions.</p>	<p>Q6A,</p> <p>Q6B, Q5C</p>
<p>S 2.5</p>	<p>Process Validation and/or Evaluation</p> <p>NCE: Process validation or evaluation studies for aseptic processing and sterilisation.</p> <p>Biotech:</p> <p>Sufficient information on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).</p> <p>Information should include a description of the plan for conducting the study and the results, analysis and conclusions from the executed study(ies). The validation of corresponding assays and analytical methods should be cross-referenced or provided (e.g. S2.4, S4.3) as part of justifying the selection of critical process controls and limits.</p> <p>For manufacturing steps, intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in A2.</p>	

Part	Data Module	Reference
S 2.6	<p>Manufacturing Process Development</p> <p>Description and discussion of significant changes made to the manufacturing process or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.</p> <p>Reference should be made to the drug substance data provided in section S4.4.</p> <p>Biotech:</p> <p>The developmental history of the manufacturing process as described in S2.2. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) including, for example, changes to the process or critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change.</p> <p>Assess significance of the change by evaluating its potential to impact the quality of the drug substance, (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches to determine impact on quality of the drug substance (see Q6B for additional guidance). A discussion of the data including a justification for selection of the tests and assessment of results.</p> <p>Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) may also include nonclinical and clinical studies. Cross-reference the location of these studies in other modules of the submission.</p>	<p>Q3A</p> <p>Q6B</p>
S 3	CHARACTERISATION	
S 3.1	<p>Elucidation of Structure and/or Biological Characterisation</p> <p>NCE: Confirmation of structure based on e.g., synthetic route and spectral analyses. Information on the potential for isomerism and the identification of stereochemistry.</p> <p>Biotech: Details on primary, secondary and higher- order structure and information on biological activity, purity, and immunochemical properties (when relevant).</p>	Q6B
S 3.2	Impurities	Q3A, Q3C, Q6A, Q6B
S 4	CONTROL OF DRUG SUBSTANCE	
S 4.1	Specification	Q6A, Q6B
S 4.2	Analytical Procedures	Q2A, Q6B
S 4.3	Validation of Analytical Procedures	Q2A, Q2B, Q6B
S 4.4	<p>Batch Analyses</p> <p>Description (including size, origin, and use) and test results of all relevant batches (e.g., nonclinical, clinical, pilot, scale-up, and, if available, production-scale batches) used to establish the specification and evaluate consistency in manufacturing.</p>	Q3A, Q3C, Q6A, Q6B

Part	Data Module	Reference
S 4.5	Justification of Specification	Q6A, Q6B
S 5	REFERENCE STANDARDS OR MATERIALS Information on the reference standards or reference materials used for testing of the drug substance and drug product.	Q6A, Q6B
S 6	CONTAINER CLOSURE SYSTEM Provide a description of the container closure systems, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate. For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. The combination of container closure specifications and drug substance stability data may be sufficient to demonstrate suitability of the container closure system for storage and shipping of the drug substance. However, for drug substances that are sensitive or reactive (e.g., hygroscopic) or in non-solid form (e.g., liquids) additional information demonstrating suitability should be provided in P2. References to any other suitability information should be placed in this section.	
S 7	STABILITY	
S 7.1	Stability Summary and Conclusions Summary of the types of studies conducted, protocols used, and the results obtained. Include results from forced degradation studies, stress conditions. Conclusions with respect to storage conditions and retest date or expiry period, as appropriate.	Q1A, Q1B, Q5C
S 7.2	Post-approval stability protocol and stability commitment	Q1A, Q5C
S 7.3	Stability Data Results of the stability studies presented in an appropriate format such as tabular, graphical, narrative. Information on analytical procedures used and their validation. Include data from forced degradation studies, stress conditions etc	Q1A, Q5C
P	DRUG PRODUCT	
P 1	DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT Description of the dosage form. Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis, including overages, if any, the function of the components, and a reference to their quality standards, e.g., compendial monographs or manufacturer's specifications. Type of container and closure used.	Q6A, Q6B
P 2	PHARMACEUTICAL DEVELOPMENT The section on Pharmaceutical Development presents information and data on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted	Q6A, Q6B

Part	Data Module	Reference
	<p>according to specifications. Additionally, this report should identify and describe the formulation and process attributes (critical parameters) that may influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature may be included within or attached to the Pharmaceutical Development report. Additional supportive data may be referenced to the relevant nonclinical or clinical sections of the application</p> <p>Reference should be made to the ICH Guidelines Q6A and Q6B when addressing, e.g., polymorphism or microbial limit testing.</p> <p>1. Components of the Drug Product</p> <p>1.1 Drug Substance</p> <p>The compatibility of the drug substance with excipients listed in P1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance, which may influence the performance of the drug product, should be discussed.</p> <p>In case of combination products, the compatibility of drug substances with each other should be discussed.</p> <p>The suitability of the container closure system (described in S 6) used for the storage, transportation (shipping) and use of drug substances that are sensitive or reactive or in non-solid form should be discussed with respect to, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance including sorption to container and leaching, and safety of materials of construction.</p> <p>1.2 Excipients</p> <p>The choice of excipients listed in P1, their concentration, and characteristics which may influence the drug product performance, should be discussed relative to their respective functions.</p> <p>2. Drug Product</p> <p>2.1 Formulation Development</p> <p>A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation described in P1 should be discussed. Results from comparative <i>in vitro</i> studies (e.g., dissolution) or comparative <i>in vivo</i> studies (e.g., bioequivalence) should be discussed when appropriate.</p> <p>2.2 Overages</p> <p>Any overages in the formulation(s) described in P1 should be justified.</p> <p>2.3 Physicochemical and Biological Properties</p> <p>Parameters relevant to the performance of the drug product such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and immunological activity should be addressed.</p> <p>3. Manufacturing Process Development</p> <p>The selection and optimisation of the manufacturing process described in P3.3, in particular its critical aspects, should be explained. Where appropriate, the</p>	

Part	Data Module	Reference
	<p>method of sterilisation should be explained and justified.</p> <p>Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P3.3, which may influence the performance of the product, should be discussed.</p> <p>4. Container Closure System</p> <p>The suitability of the container closure system (described in P6) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form including sorption to container and leaching, safety of materials of construction, and performance such as reproducibility of the dose delivery from the device when presented as part of the drug product.</p> <p>5. Microbiological Attributes</p> <p>Where appropriate, the microbiological attributes of the dosage form should be discussed including the rationale for not performing microbial limits testing for non-sterile products, and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.</p> <p>6. Compatibility</p> <p>The compatibility of the drug product with dosage devices, e.g., precipitation of drug substance in solution, sorption on injection vessels, should be addressed to provide appropriate and supportive information for the labelling.</p>	
P 3	MANUFACTURE	
P 3.1	<p>Manufacturer(s)</p> <p>Name, address, and responsibility for each manufacturer including contractors, and each proposed production site or facility involved in manufacture and testing.</p>	---
P 3.2	<p>Batch Formula</p> <p>List of all components of the dosage form to be used in the manufacturing process, and their amounts on a per batch basis, including overages, and a reference to quality standards.</p>	---
P 3.3	<p>Description of Manufacturing Process and Process Controls</p> <p>A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.</p> <p>A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies, and packaging operations that directly affect product quality, should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity.</p> <p>Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values may be presented as an expected range. Numeric ranges for critical steps should be justified in Section P3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent</p>	Q6B

Part	Data Module	Reference
	<p>product) should be stated.</p> <p>Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (P3.3).</p> <p>Additionally for Biotech see A1 for facilities, if appropriate.</p>	
P 3.4	<p>Controls of Critical Steps and Intermediates</p> <p>Critical Steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to assure that the process is controlled.</p> <p>Intermediates: Specifications and analytical procedures, if any, for intermediates including validation of analytical procedures, where appropriate.</p>	Q6A, Q6B, Q2A, Q2B
P 3.5	<p>Process Validation and/or Evaluation</p> <p>Description, documentation, and results of the validation or evaluation studies for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation in A2, if necessary.</p>	Q6B
P 4	CONTROL OF EXCIPIENTS	
P 4.1	Specifications	Q6B
P 4.2	Analytical Procedures	Q2A, Q6B
P 4.3	Validation of Analytical Procedures	Q2A, Q2B, Q6B
P 4.4	Justification of Specifications	Q3C, Q6B
P 4.5	<p>Excipients of Human or Animal Origin</p> <p>For excipients of human or animal origin, provide information regarding adventitious agents (e.g., specifications; description of the testing performed; viral safety data, details in A2).</p>	Q5A, Q5D, Q6B
P 4.6	<p>Novel Excipients</p> <p>Excipient(s) used for the first time in a drug product or by a new route of administration. Full details of manufacture, characterisation, and controls as for new drug substances, with cross references to supporting safety (nonclinical and/or clinical) data.</p>	---
P 5	CONTROL OF DRUG PRODUCT	
P 5.1	Specification	Q6A, Q6B
P 5.2	Analytical Procedures	Q2A
P 5.3	Validation of Analytical Procedures	Q2A, Q2B
P 5.4	<p>Batch Analyses</p> <p>Description (including size, origin, and use) and test results of all relevant batches (e.g., nonclinical, clinical, pilot, scale-up, and, if available, production-scale batches) used to establish specifications and evaluate consistency in manufacturing.</p>	Q3B, Q3C, Q6A, Q6B
P 5.5	Justification of Specification	Q6A, Q3B Q6B
P 6	CONTAINER CLOSURE SYSTEM	

Part	Data Module	Reference
	<p>Provide a description of the container closure systems, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate.</p> <p>For non-functional secondary packaging components (e.g., those that do not provide additional protection nor serve to deliver the product) only a brief description should be provided. For functional secondary packaging components, additional information should be provided.</p> <p>The combination of container closure specifications and drug product stability data may be sufficient to demonstrate suitability of the container closure system for the storage and shipment of the drug product. However, for drug products that are sensitive or reactive (e.g., hygroscopic) or in non-solid form (e.g., liquids, suspensions) additional information demonstrating suitability should be provided in P2. References to any other suitability information should be placed in this section, P6.</p>	
P 7	STABILITY	
P 7.1	<p>Stability Summary and Conclusions</p> <p>A summary discussing the types of studies conducted, protocols used and the results obtained. Conclusions with respect to storage conditions and expiry period, and, if applicable, in-use storage conditions and expiry period.</p>	Q1A, Q1B, Q5C
P 7.2	<p>Post-approval Stability Protocol and Stability Commitment</p>	Q1A, Q5C
P 7.3	<p>Stability Data</p> <p>Results of the stability studies presented in an appropriate format such as tabular, graphical, narrative. Information on analytical procedures used and their validation.</p>	Q1A, Q5C
R	REGIONAL INFORMATION (REFER TO REGIONAL GUIDELINES)	
R 1	Executed Batch Records (USA only)	---
R 2	Method Validation Package (USA only)	---
R 3	Comparability Protocols (USA only)	
R 4	<p>Process Validation Protocol of the Drug Product (EU)</p> <p>Where validation is still to be completed, a summary of the studies intended to be conducted.</p>	---
A	APPENDICES	
A 1	<p>BIOTECH FACILITIES AND EQUIPMENT</p> <p>A diagram that illustrates the flow for manufacture of the product, including movement of raw materials, personnel, waste, and intermediate(s), in and out of the manufacturing areas. Presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.</p> <p>Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product.</p> <p>A summary description of product-contact equipment, its use (dedicated or multi-use) and information on preparation, cleaning, sterilisation, and storage of specified equipment and materials, as appropriate.</p>	---

Part	Data Module	Reference
	<p>Information on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination for areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.</p>	
<p>A 2</p>	<p>VIRAL SAFETY EVALUATION</p> <p>This section is intended to provide detailed information from viral safety evaluation studies. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, Q5D, and Q6B for further guidance.</p> <p>Materials of Biological Origin</p> <p>Information necessary to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines). Related information in S2.3, and P4.5.</p> <p>In addition for cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells, and viral qualification of cell banks. Related information in S2.3.</p> <p>Viral Testing of Unprocessed Bulk</p> <p>In accordance with Q5A, results for viral testing of unprocessed bulk.</p> <p>Viral Clearance Studies</p> <p>In accordance with Q5A, the rationale and action plan for assessing viral clearance and results and evaluation of the viral clearance studies. Data may include those which demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. Related information in S2.5 and P3.5.</p> <p>Testing at appropriate stages of production</p> <p>The selection of virological tests, which are conducted during manufacturing, e.g., cell substrate, unprocessed bulk or post viral clearance testing, should be justified. Include the type of test, sensitivity and specificity of the test, if applicable, and frequency of testing. Test results to confirm, at an appropriate stage of manufacture, the product is free from viral contamination. Related information in S2.4 and P3.4 and S4 and P5.</p>	<p>Q5A</p>