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

ICH HARMONISED TRIPARTITE GUIDELINE

THE COMMON TECHNICAL DOCUMENT

MODULE 2 : QUALITY OVERALL SUMMARY (QOS)
MODULE 3 : QUALITY

Recommended for Adoption

at Step 4 of the ICH Process

on 9 November 2000

by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

THE COMMON TECHNICAL DOCUMENT
QUALITY

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 9 November 2000, this guideline is recommended for adoption to the three regulatory parties to ICH

MODULE 2 :
QUALITY OVERALL SUMMARY (QOS)

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

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

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

The *italicised* text below indicates where tables, figures, or other items can be imported directly from Module 3.

INTRODUCTION

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

S DRUG SUBSTANCE

S1 General Information

Information from S1 should be included.

S2 Manufacture

Information from S2 should be included:

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

- *A flow diagram, as provided in S2.2;*
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in S2.3;
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in S2.4;
- A description of process validation and/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 non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

S3 Characterisation

For NCE:

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

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 that 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, should be included.

For NCE and Biotech:

The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in S3.2, with graphical representation, where appropriate should be included.

S4 Control of Drug Substance

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

Specification from S4.1 should be provided.

A tabulated summary of the batch analyses from S4.4, with graphical representation where appropriate, should be provided.

S5 Reference Standards or Materials

Information from S5 (tabulated presentation, where appropriate) should be included.

S6 Container Closure System

A brief description and discussion of the information, from S6 should be included.

S7 Stability

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in S7.1.

The post-approval stability protocol, as described in S7.2, should be included.

A tabulated summary of the stability results from S7.3, with graphical representation where appropriate, should be provided.

P DRUG PRODUCT

P1 Description and Composition of the Drug Product

Information from P1 should be provided.

Composition from P1 should be provided.

P2 Pharmaceutical Development

A discussion of the information and data from P2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

P3 Manufacture

Information from P3 should include:

- 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.*
- A brief description of the process validation and/or evaluation, as described in P3.5.

P4 Control of Excipients

A brief summary on the quality of excipients, as described in P4, should be included.

P5 Control of Drug Product

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

Specification(s) from P5.1 should be provided.

A tabulated summary of the batch analyses provided under P5.4, with graphical representation where appropriate, should be included.

P6 Reference Standards or Materials

Information from P6 (tabulated presentation, where appropriate) should be included.

P7 Container Closure System

A brief description and discussion of the information in P7 should be included.

P8 Stability

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.

A tabulated summary of the stability results from P8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in P8.2, should be provided.

A APPENDICES

A1 Facilities and Equipment

Biotech:

A summary of facility information described under A1 should be included.

A2 Adventitious Agents Safety Evaluation

A discussion on measures implemented to control endogenous and adventitious agents in production should be included.

A tabulated summary of the reduction factors for viral clearance from A2, should be provided.

R REGIONAL INFORMATION

A brief description of the information specific for the region, as provided under "R" should be included, where appropriate.

THE COMMON TECHNICAL DOCUMENT

MODULE 3 :
QUALITY

TABLE OF CONTENTS

1. SCOPE OF THE GUIDELINE

This document is intended to provide guidance on the format of a registration application 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.

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

The section titles of Part R (Regional Information) represent examples of typical topics of information that are not common to all ICH regions. Hence, the information to be provided in these sections should be based on the relevant regional guidelines.

2. MODULE 3 FORMAT

A. TABLE OF CONTENTS

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

B. BODY OF DATA

S DRUG SUBSTANCE

S 1 General Information

S 1.1 Nomenclature

Information on the nomenclature of the drug substance should be provided. For example:

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

S 1.2 Structure

NCE:

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

Biotech:

The schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.

Reference ICH Guidelines: Q6A and Q6B

S 2 Manufacture

S 2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

S 2.2 Description of Manufacturing Process and Process Controls

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example:

NCE:

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).

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.

Biotech:

Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.

<u>Batch(es) and scale definition</u>

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

<u>Cell culture and harvest</u>

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g. cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps(i.e., unit operations) and intermediates. Relevant information for each stage, such as

population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in S2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in S2.3); major equipment (details provided in A1); and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in S2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in S2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e, unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in S2.4 should be identified.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in S2.3, major equipment (details provided in A1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Equipment details in A1; validation studies for the reuse and regeneration of columns and membranes in S2.5.) The description should includes process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates. (Details in S2.4.)

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in S2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in S2.4.).

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in S2.4.) The container closure system(s) used for storage of the drug substance (details in S 6.) and storage and shipping conditions for the drug substance should be described.

Reference ICH Guidelines: Q5A, Q5B, and Q6B

S 2.3 Control of Materials

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced

materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterisation. (Details in A2 for both NCE and Biotech)

Reference ICH Guidelines: Q6A and Q6B

Biotech:

Control of Source and Starting Materials of Biological Origin

Summaries of viral safety information for biologically-sourced materials should be provided. (Details in A2.)

Source, history, and generation of the cell substrate

Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in Q5B and Q5D.

Cell banking system, characterisation, and testing

Information on the cell banking system, quality control activities, and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided as described in Q5B and Q5D.

Reference ICH Guidelines: Q5A, Q5B, Q5C and Q5D

S 2.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in S2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Reference ICH Guidelines: Q6A and Q6B

Additionally for Biotech: Stability data supporting storage conditions should be provided.

Reference ICH Guideline: Q5C

S 2.5 Process Validation and/or Evaluation

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

Biotech:

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

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., S2.4, S4.3)

or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in A2.

S 2.6 Manufacturing Process Development

NCE:

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section S4.4.

Reference ICH Guideline: Q3A

Biotech:

The developmental history of the manufacturing process, as described in S2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance (see Q6B for additional guidance). A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

Reference should be made to the drug substance data provided in section S4.4.

Reference ICH Guideline: Q6B

S 3 Characterisation

S 3.1 Elucidation of Structure and other Characteristics

NCE:

Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Reference ICH Guideline: Q6A

Biotech:

For desired product and product-related substances, details should be provided on primary, secondary and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant.

Reference ICH Guideline: Q6B

S 3.2 Impurities

Information on impurities should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q5C, Q6A, and Q6B

S 4 Control of Drug Substance

S 4.1 Specification

The specification for the drug substance should be provided.

Reference ICH Guidelines: Q6A and Q6B

S 4.2 Analytical Procedures

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

Reference ICH Guidelines: Q2A and Q6B

S 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

Reference ICH Guidelines: Q2A, Q2B, and Q6B

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q6A, and Q6B

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q6A and Q6B

S 5 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

Reference ICH Guidelines: Q6A and Q6B

S 6 Container Closure System

A description of the container closure system(s) should be provided, 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 suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance ,including sorption to container and leaching, and/or safety of materials of construction.

S 7 Stability

S 7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference ICH Guidelines: Q1A, Q1B, and Q5C

S 7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A and Q5C

S 7.3 Stability Data

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference ICH Guidelines: Q1A, Q1B, Q2A, Q2B, and Q5C

P DRUG PRODUCT

P 1 Description and Composition of the Drug Product

A description of the drug product and its composition should be provided. The information provided should include, for example:

- Description of the dosage form;
- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis(including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)
- Description of accompanying reconstitution diluent(s); and
- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Reference ICH Guidelines: Q6A and Q6B

P 2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage

instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

Reference ICH Guidelines: Q6A and Q6B

P 2.1 Components of the Drug Product

P 2.1.1 Drug Substance

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 that can influence the performance of the drug product should be discussed.

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

P 2.1.2 Excipients

The choice of excipients listed in P1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

P 2.2 Drug Product

P 2.2.1 Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in P1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

P 2.2.2 Overages

Any overages in the formulation(s) described in P1 should be justified.

P 2.2.3 Physicochemical and Biological Properties

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

P 2.3 Manufacturing Process Development

The selection and optimisation of the manufacturing process described in P3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P3.3 that can influence the performance of the product should be discussed.

P 2.4 Container Closure System

The suitability of the container closure system (described in P7) 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 2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

P 2.6 Compatibility

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

P 3 Manufacture

P 3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

P 3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

P 3.3 Description of Manufacturing Process and Process Controls

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.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section P3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

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).

Additionally for Biotech see A1 for facilities, if appropriate.

Reference ICH Guideline: Q6B

P 3.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in P3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Reference ICH Guidelines: Q2A, Q2B, Q6A, and Q6B

P 3.5 Process Validation and/or Evaluation

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in A2, if necessary.

Reference ICH Guideline: Q6B

P 4 Control of Excipients

P 4.1 Specifications

The specifications for excipients should be provided.

Reference ICH Guideline: Q6A and Q6B

P 4.2 Analytical Procedures

The analytical procedures used for testing the excipients should be provided, where appropriate.

Reference ICH Guidelines: Q2A and Q6B

P 4.3 Validation of Analytical Procedures

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B

P 4.4 Justification of Specifications

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

Reference ICH Guidelines: Q3C and Q6B

P 4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). (Details in A2).

Reference ICH Guidelines: Q5A, Q5D, and Q6B

P 4.6 Novel Excipients

For 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, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format

P 5 Control of Drug Product

P 5.1 Specification(s)

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

Reference ICH Guidelines: Q3B, Q6A and Q6B

P 5.2 Analytical Procedures

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

Reference ICH Guidelines: Q2A and Q6B

P 5.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.

Reference ICH Guidelines: Q2A, Q2B and Q6B.

P 5.4 Batch Analyses

A description of batches and results of batch analyses should be provided.

Reference ICH Guidelines: Q3B, Q3C, Q6A, and Q6B

P 5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in "S 3.2 Impurities".

Reference ICH Guidelines: Q3B, Q5C, Q6A, and Q6B

P 5.6 Justification of Specification(s)

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

Reference ICH Guidelines: Q3B, Q6A, and Q6B

P 6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "S 5 Reference Standards or Materials".

Reference ICH Guidelines: Q6A and Q6B

P 7 Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate.

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

Suitability information should be located in P 2.

P 8 Stability

P 8.1 Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

Reference ICH Guidelines: Q1A, Q1B, Q3B, and Q5C, Q6A

P 8.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A and Q5C

P 8.3 Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterisation of impurities is located in P 5.5.

Reference ICH Guidelines: Q1A , Q1B, Q2A, Q2B and Q5C

A APPENDICES

A 1 Facilities and Equipment

Biotech:

A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

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

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

A 2 Adventitious Agents Safety Evaluation

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

For non-viral adventitious agents:

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

Reference ICH Guidelines: Q5A, Q5D, and Q6B

For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production 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.

Materials of Biological Origin

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in S2.3, and P4.5). For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in S2.3).

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in S2.4 and P3.4).

Viral Testing of Unprocessed Bulk

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral Clearance Studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in S2.5 and P3.5).

Reference ICH Guidelines: Q5A, Q5D, and Q6B

R REGIONAL INFORMATION

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

Some examples are as follows:

- **Executed Batch Records (USA only)**
- **Method Validation Package (USA only)**
- **Comparability Protocols (USA only)**
- **Process Validation Scheme for the Drug Product (EU only)**

Where validation is still to be completed, a summary of the studies intended to be conducted should be provided.

- **Medical Device (EU only)**

C KEY LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.