Guidance for Industry

M4Q: The CTD — Quality

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2001
ICH

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M4Q: CTD — Quality

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TABLE OF CONTENTS

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This guidance represents the Food and Drug Administration's (FDA'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 and regulations.

INTRODUCTION

This is one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the U.S. Food and Drug Administration (FDA). This guidance presents the agreed upon common format for the preparation of a well-structured Quality section of the CTD for applications that will be submitted to regulatory authorities. A common format for the technical documentation will significantly reduce the time and resources used to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information among regulatory authorities will be simplified.

For information on the Safety and Efficacy sections of the CTD, see the individual guidances for industry that discuss those parts of the CTD. For general information about the CTD, as well as specific information about Module 1 (regional administrative information), see the guidance for industry, *General Considerations for Submitting Marketing Applications According to the ICH/CTD Format.* [2] The CTD guidances are intended to be used together with other ICH and Agency guidances. Please refer to those guidances for detailed information about the *contents* of an application.

[1] This guidance was developed within the Expert Working Group on Quality of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2000. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] A draft version of the General Considerations guidance is currently available. Once it has been finalized, it will represent the Agency's thinking on this topic.

BACKGROUND

The CTD

Through the ICH process, considerable harmonization has been achieved among the three regions (Japan, Europe, and the United States) in the technical requirements for the registration of pharmaceuticals for human use. However, until now, there has been no harmonization of the organization of a submission. Each region has its own requirements for the organization of the technical reports in the submission and for the preparation of the summaries and tables. In Japan, the applicants must prepare the *GAIYO*, which organizes and presents a summary of the technical information. In Europe, expert reports and tabulated summaries are required, and written summaries are recommended. The U.S. FDA has guidance regarding the format and content of the new drug application submission. To avoid generating and compiling different registration dossiers, this guidance describes a format for the Quality section of the CTD that will be acceptable in all three regions.

Preparing and Organizing the CTD

This guidance primarily addresses the organization of the information to be presented in the Quality section of an application for new pharmaceuticals (including biotechnology-derived products). Guidances also are available that discuss the Safety and Efficacy sections of the CTD. These guidances are not intended to indicate what studies are required. The guidances merely indicate an appropriate *format* for the data that have been acquired. Applicants should not modify the overall organization of the CTD. However, in the Nonclinical and Clinical Summaries sections of the CTD, applicants can modify individual formats to provide the best possible presentation of the technical information to facilitate the understanding and evaluation of the results.

Throughout the CTD, the display of information should be unambiguous and transparent, to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5 x 11" paper (U.S.). The left-hand margin should be sufficiently large that information is not obscured through binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text. Acronyms and abbreviations should be defined the first time they are used in each module. References should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE).[3]

The CTD should be organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with the CTD guidances should

[3] The first edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* was conceived by the Vancouver Group and was published in 1979.

help ensure that these four modules are provided in a format acceptable to the regulatory authorities (see the figure and overall outline on the following pages).

Module 1. Administrative Information and Prescribing Information
This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities. For information about this module see the guidance for industry, *General Considerations for Submitting Marketing Applications According to the ICH/CTD Format*.

Module 2. Common Technical Document Summaries
Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the introduction should not exceed one page.

Module 2 should contain 7 sections in the following order:

- CTD Table of Contents
- CTD Introduction
- Quality Overall Summary
- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
- Clinical Summary.

The individual organization of the Module 2 summaries is described in three separate documents:

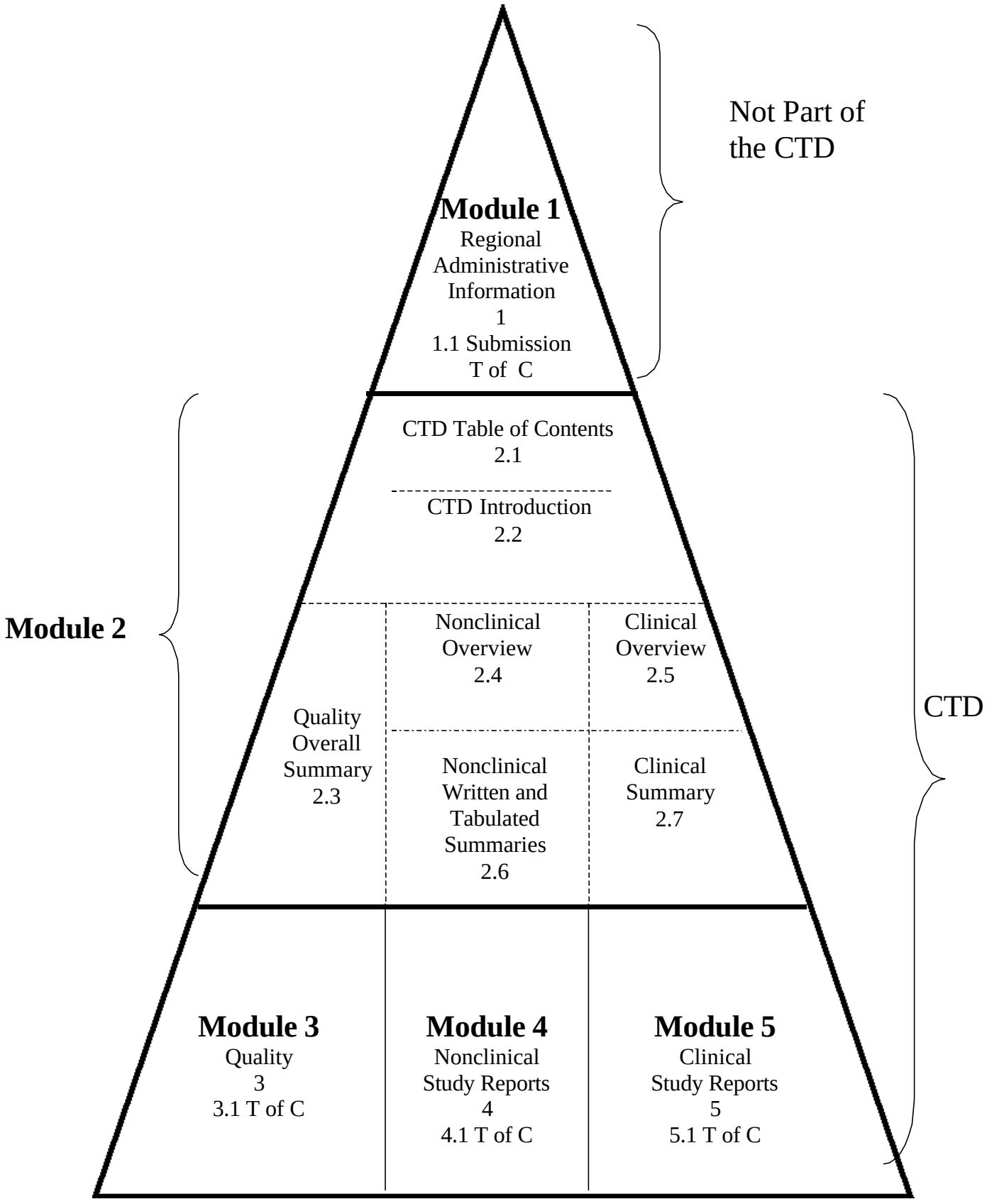
- *M4Q: The CTD — Quality*
- *M4S: The CTD — Safety*
- *M4E: The CTD — Efficacy*.

Module 3. Quality
Information on Quality should be presented in the structured format described in the guidance M4Q.

Module 4. Nonclinical Study Reports
The Nonclinical Study Reports should be presented in the order described in the guidance M4S.

Module 5. Clinical Study Reports
The human study reports and related information should be presented in the order described in the guidance M4E .

Diagrammatic Representation of the ICH Common Technical Document



The CTD should be organized according to the following general outline.

Module 1: Administrative Information and Prescribing Information

1.1 Table of Contents of the Submission Including Module 1
1.2 Documents Specific to Each Region (for example, application forms, prescribing information)

Module 2: Common Technical Document Summaries

2.1 CTD Table of Contents
2.2 CTD Introduction
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summary
Pharmacology
Pharmacokinetics
Toxicology
2.7 Clinical Summary
Biopharmaceutics and Associated Analytical Methods
Clinical Pharmacology Studies
Clinical Efficacy
Clinical Safety
Synopses of Individual Studies

Module 3: Quality

3.1 Module 3 Table of Contents
3.2 Body of Data
3.3 Literature References

Module 4: Nonclinical Study Reports

4.1 Module 4 Table of Contents
4.2 Study Reports
4.3 Literature References

Module 5: Clinical Study Reports

5.1 Module 5 Table of Contents
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

Organization and Format of the ICH Guidances for Industry

Although the CTD is organized by modules, the guidances for industry that provide recommendations for applicants on preparing the CTD have been organized by topic: Quality, Safety, and Efficacy. As a result, guidance discussing Module 2 is divided among three guidances.

- Guidance on the Quality section of the CTD (Module 2, Quality Overall Summary (QOS), and Module 3) can be found in the guidance for industry *M4Q: The CTD — Quality.*

- Guidance on the Safety section of the CTD (Module 2, the Nonclinical Overview and the Nonclinical Written and Tabulated Summaries, and Module 4) can be found in the guidance for industry *M4S: The CTD — Safety*

- Guidance on the Efficacy section of the CTD (Module 2, the Clinical Overview and the Clinical Summary, and Module 5) can be found in the guidance for industry *M4E: The CTD — Efficacy*.

Numbering

In the guidances for industry on the Quality, Safety, and Efficacy sections of the CTD, Arabic numbers have been assigned to designate those specific sections that should be included in the CTD. The Arabic numbers used in the guidances also should be used when assembling the CTD for submission. For specific information on numbering the pages and volumes of the submission, see the guidance for industry, *General Considerations for Submitting Marketing Applications According to the ICH/CTD Format*. Sections in the guidance documents that are not numbered provide guidance on how to prepare those sections. In this guidance for industry, sections that should be included in Module 2 and Module 3 of the CTD have been numbered using the Arabic numbers 2 and 3, respectively.

It is possible that information for more than one drug substance or drug product will be submitted. In such cases, please continue the use of Arabic numbers by repeating the specific section's numbering, making it clear that the data are for an additional drug substance or drug product. For example, for an additional drug substance (2.3.S), repeat section 2.3.S and include the name of the additional substance (e.g., 2.3.S [name of drug substance]. The same approach should be used for an additional drug product (e.g., 2.3.P [name of drug product] and, in the Efficacy section of the CTD application, for an additional indication (e.g., 2.7.3 pneumonia, 2.7.3 URI).

MODULE 2 QUALITY OVERALL SUMMARY

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 emphasize critical key parameters of the product and provide, for instance, justification in cases where guidance was 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 by toxicological studies discussed under the M4S 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).

Most of the information requested in the QOS, including tables, figures, or other items and whether specified in the following text or not, can be imported directly from Module 3.

2.3 INTRODUCTION TO THE QUALITY OVERALL SUMMARY

The introduction should include proprietary name, nonproprietary name or common name of the drug substance, company name, dosage forms, strengths, route of administration, and proposed indications.

2.3.S DRUG SUBSTANCE [NAME, MANUFACTURER]

2.3.S.1 General Information [name, manufacturer]

Information from 3.2.S.1 section of Module 3 should be included here.

2.3.S.2 Manufacture [name, manufacturer]

Information from section 3.2.S.2 of Module 3 that should be provided includes

- 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 materials of appropriate quality
- A flow diagram, as provided in 3.2.S.2.2 of Module 3, should be imported directly
- A description of the source and starting material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3 of Module 3

- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4 of Module 3
- A description of process validation and/or evaluation, as described in 3.2.S.2.5 of Module 3
- A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6 of Module 3. The QOS should also cross-reference the nonclinical and clinical studies that used batches affected by these manufacturing changes, as provided in the M4S and M4E sections of the application.

2.3.S.3 Characterization [name, manufacturer]

For New Chemical Entities (NCE):

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included.

When a drug substance is chiral, please specify 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 characterization data (for example, primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.

For NCE and Biotech:

The QOS should summarize the data on potential and actual impurities arising from the synthesis, manufacture, and/or degradation and should summarize the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarize 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. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.S.3.2, with graphic representation where appropriate, should be imported directly.

2.3.S.4 Control of Drug Substance [name, manufacturer]

A brief summary of the justification of the specifications, the analytical procedures, and validation should be included.

Specification from 3.2.S.4.1 of Module 3 should be imported directly.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphic representation where appropriate, should be imported directly.

2.3.S.5 Reference Standards or Materials [name, manufacturer]

Information from 3.2.S.5 of Module 3 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System [name, manufacturer]

A brief description and discussion of the information from 3.2.S.6 of Module 3 should be included.

2.3.S.7 Stability [name, manufacturer]

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, and the retest date or shelf life, where relevant, as described in 3.2.S.7.1.

The postapproval stability protocol, as described in 3.2.7.2 S of Module 3, should be included.

A tabulated summary of the stability results from 3.2.S.7.3 of Module 3, with graphic representation where appropriate, should be imported directly.

***Note**: A separate section 2.3.S should be provided for each drug substance. For example, for a second substance, the sections would be labeled 2.3.S [name 2, manufacturer]. For a substance coming from another manufacturer, the sections would be labeled 2.3.S [name, manufacturer 2]*.

2.3.P DRUG PRODUCT [NAME, DOSAGE FORM]

2.3.P.1 Description and Composition of the Drug Product

Information from 3.2.P.1 of Module 3 should be provided. Composition from 3.2.P.1 of Module 3 should be imported directly.

2.3.P.2 Pharmaceutical Development [name, dosage form]

A discussion of the information and data from 3.2.P.2 of Module 3 should be presented. A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be imported directly, where relevant.

2.3.P.3 Manufacture [name, dosage form]

Information from 3.2.P.3 of Module 3 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 a product of appropriate quality
- A flow diagram, as provided under 3.2.P.3.3, should be imported directly
- A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5 of Module 3

2.3.P.4 Control of Excipients [name, dosage form]

A brief summary of the quality of excipients, as described in 3.2.P.4 of Module 3, should be included.

2.3.P.5 Control of Drug Product [name, dosage form]

A brief summary of the justification of the specifications, a summary of the analytical procedures and validation, and characterization of impurities should be provided.

Specifications from 3.2.P.5.1 of Module 3 should be imported directly.

A tabulated summary of the batch analyses provided under 3.2.P.5.4 of Module 3, with graphic representation where appropriate, should be imported directly.

2.3.P.6 Reference Standards or Materials [name, dosage form]

Information from 3.2.P.6 of Module 3 (tabulated presentation where appropriate) should be included.

2.3.P.7 Container Closure System [name, dosage form]

A brief description and discussion of the information in 3.2.P.7 of Module 3 should be included.

2.3.P.8 Stability [name, dosage form]

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions regarding 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 3.2.P.8.3, with graphic representation where appropriate, should be imported directly.

The postapproval stability protocol, as described in 3.2.P.8.2, should be provided.

Note: *A separate section 2.3.P should be provided for each dosage form. For example, for a second dosage form, the sections would be labeled 2.3.P [name, dosage form 2].*

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment

For Biotech:

A summary of facility information described under Appendix 3.2.A.1, the Facilities and Equipment section of Module 3, should be included.

2.3.A.2. Adventitious Agents Safety Evaluation

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

A tabulated summary of the reduction factors for viral clearance from Appendix 3.2.A.2, the Adventitious Agents Safety Evaluation section of Module 3, should be imported directly.

2.3.A.3 Novel Excipients

A brief discussion of information described under 3.2.A.3 should be included.

2.3.R REGIONAL INFORMATION

A brief description of the information specific to the region as provided under 3.2.R *Regional* in Module 3 should be included, where appropriate.

MODULE 3: FORMAT OF THE QUALITY SECTION OF THE CTD

This section of the 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 ICH guidances Q6A New Chemical Entities (NCE) and Q6B Biological/Biotechnological (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 guidances, but harmonized content is not available for all sections. The Body of Data section in this guidance merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this guidance, and both may depend on regional guidance.

The section titles listed in the Regional Information section (3.2.R) 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 guidance.

Guidances Referenced in this Section

Q1A *Stability Testing of New Drug Substances and Products* (September 1994)

Q1B *Photostability Testing of New Drug Substances and Products* (November 1996)

Q2A *Text on Validation of Analytical Procedures* (March 1995)

Q2B *Validation of Analytical Procedures: Methodology* (November 1996)

Q3A *Impurities in New Drug Substances* (January 1996)

Q3B *Impurities in New Drug Products* (November 1996)

Q3C *Impurities: Residual Solvents* (December 1997)

Q5A *Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin* (September 1998)

Q5B *Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products* (February 1996)

Q5C *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996)

Q5D *Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* (September 1998)

Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000)

Q6B *Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999)

3.1 MODULE 3 TABLE OF CONTENTS

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

3.2 BODY OF DATA

3.2.S DRUG SUBSTANCE [NAME, MANUFACTURER][4]

3.2.S.1 General Information [name, manufacturer]

3.2.S.1.1 Nomenclature[name, manufacturer]

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

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

3.2.S.1.2 Structure[name, manufacturer]

For NCE:

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

For Biotech:

[4] For a drug product containing more than one drug substance, the information requested for part S should be provided in its entirety for each drug substance.

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

3.2.S.1.3 General Properties[name, manufacturer]

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

Reference ICH guidances Q6A and Q6B.

3.2.S.2 Manufacture [name, manufacturer]

3.2.S.2.1 Manufacturers[name, manufacturer]

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

3.2.S.2.2 Description of Manufacturing Process and Process Controls [name, manufacturer]

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

For NCE:

A flow diagram of the synthetic processes should be provided that includes molecular formulas, weights, yield ranges, chemical structures of starting materials, intermediates, reagents, and drug substance reflecting stereochemistry, and that 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 3.2.S.2.5.

For Biotech:

Information should be provided on the manufacturing process, which typically starts with vials of the cell bank and includes cell culture, harvests, purification and modification reactions, filling, storage, and shipping conditions.

Batches and scale definition

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

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g., cells contained in one or more vials 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 3.2.S.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included, for example, on scale; culture media and other additives (provide details in 2.3.S); major equipment (provide details in Appendix 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment, and intermediates with acceptance criteria (provide details in 3.2.S.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and on shipping and storage conditions should be provided. (Provide details on shipping and storage in 3.2.S.2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvests 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, selection of fraction, and storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 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 (provide details in 3.2.S.2.3), major equipment (provide details in Appendix 3.2.A.1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Provide equipment details in Appendix 3.2.A.1; provide validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment, and intermediates. (Provide details in 3.2.S.2.4.)

Reprocessing procedures with criteria for the reprocessing of any intermediate or the drug substance should be described. (Provide details in 3.2.S.2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and on shipping and storage conditions should be provided (provide details on shipping and storage in 3.2.S.2.4).

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 (provide details in 3.2.S.2.4). The container closure systems used for storage of the drug substance (3.2.S.6.) and storage and shipping conditions for the drug substance should be described.

Reference ICH guidances Q5A, Q5B, and Q6B.

3.2.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 on the source, manufacture, and characterization. (Provide details in Appendix 3.2.A.2 for both NCE and Biotech.)

Reference ICH guidances Q6A and Q6B.

<u>For Biotech:</u>

Control of Source and Starting Materials of Biological Origin

Summaries of viral safety information for biologically sourced materials should be provided. (Provide details in the Adventitious Agents Safety Evaluation section of the Appendix 3.2.A.2.)

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 ICH guidances Q5B and Q5D.

Cell banking system, characterization, 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 banks) should be provided as described in Q5B and Q5D.

Reference ICH guidances Q5A, Q5B, Q5C, and Q5D.

3.2.S.2.4 Controls of Critical Steps and Intermediates [name, manufacturer]

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

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

Reference ICH guidances Q6A and Q6B.

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

Reference ICH guidance Q5C.

3.2.S.2.5 Process Validation and/or Evaluation[name, manufacturer]

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

For 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 studies should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in Appendix 3.2.A.2.

3.2.S.2.6 Manufacturing Process Development [name, manufacturer]

For 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 3.2.S.4.4.

Reference ICH guidance Q3A.

For Biotech:

The developmental history of the manufacturing process, as described in 3.2.S.2.2, should be provided. The description of changes 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 substances and the corresponding drug products 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 3.2.S.4.4.

Reference ICH guidance Q6B.

3.2.S.3 Characterization [name, manufacturer]

3.2.S.3.1 Elucidation of Structure and other Characteristics [name, manufacturer]

For NCE:

Confirmation of structure based on, for example, 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 guidance Q6A.

For Biotech:

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

Reference ICH guidance Q6B.

3.2.S.3.2 Impurities [name, manufacturer]

Information on impurities should be provided.

Reference ICH guidances Q3A, Q3C, Q5C, Q6A, and Q6B.

3.2.S.4 Control of Drug Substance [name, manufacturer]

3.2.S.4.1 Specification [name, manufacturer]

The specification for the drug substance should be provided.

Reference ICH guidances Q6A and Q6B.

3.2.S.4.2 Analytical Procedures [name, manufacturer]

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

Reference ICH guidances Q2A and Q6B.

3.2.S.4.3 Validation of Analytical Procedures [name, manufacturer]

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

Reference ICH guidances Q2A, Q2B, and Q6B.

3.2.S.4.4 Batch Analyses [name, manufacturer]

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

Reference ICH guidances Q3A, Q3C, Q6A, and Q6B.

3.2.S.4.5 Justification of Specification [name, manufacturer]

Justification for the drug substance specification should be provided.

Reference ICH guidances Q3A, Q3C, Q6A, and Q6B.

3.2.S.5 Reference Standards or Materials [name, manufacturer]

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

Reference ICH guidances Q6A and Q6B.

3.2.S.6 Container Closure System [name, manufacturer]

A description of the container closure systems 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). Noncompendial methods (with validation) should be included, where appropriate.

For nonfunctional 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.

3.2.S.7 Stability [name, manufacturer]

3.2.S.7.1 Stability Summary and Conclusions [name, manufacturer]

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

Reference ICH guidances Q1A, Q1B, and Q5C.

3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment [name, manufacturer]

The postapproval stability protocol and stability commitment should be provided.

Reference ICH guidances Q1A and Q5C.

3.2.S.7.3 Stability Data [name, manufacturer]

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

Reference ICH guidances Q1A, Q1B, Q2A, Q2B, and Q5C.

3.2.P DRUG PRODUCT [NAME, DOSAGE FORM]

3.2.P.1 Description and Composition of the Drug Product [name dosage form]

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

- 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[5] of accompanying reconstitution diluents
- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable

Reference ICH guidances Q6A and Q6B.

3.2.P.2 Pharmaceutical Development [name, dosage form]

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application. The studies described in this section should be 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 guidances Q6A and Q6B.

3.2.P.2.1 Components of the Drug Product [name, dosage form]

3.2.P.2.1.1 Drug Substance [name, dosage form]

The compatibility of the drug substance with the excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.

[5] For a drug product supplied with reconstitution diluents, information on the diluents should be provided in a separate part P, as appropriate.

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

3.2.P.2.1.2 Excipients[name, dosage form]

The choice of excipients listed in 3.2.P.1, their concentration, and the characteristics that can influence the drug product performance should be discussed relative to their respective functions.

3.2.P.2.2 Drug Product [name, dosage form]

3.2.P.2.2.1 Formulation Development [name, dosage form]

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e., composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

3.2.P.2.2.2 Overages [name, dosage form]

Any overages in the formulations described in P1 should be justified.

3.2.P.2.2.3 Physicochemical and Biological Properties [name, dosage form]

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

3.2.P.2.3 Manufacturing Process Development [name, dosage form]

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Differences between the manufacturing processes used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

3.2.P.2.4 Container Closure System [name, dosage form]

The suitability of the container closure system (described in 3.2.P.7) for the storage, transportation (shipping), and use of the drug product should be discussed. This discussion should consider, for example, 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).

3.2.P.2.5 Microbiological Attributes [name, dosage form]

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for nonsterile 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.

3.2.P.2.6 Compatibility[name, dosage form]

The compatibility of the drug product with reconstitution diluents 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.

3.2.P.3 Manufacture [name, dosage form]

3.2.P.3.1 Manufacturers [name, dosage form]

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

3.2.P.3.2 Batch Formula [name, dosage form]

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

3.2.P.3.3 Description of Manufacturing Process and Process Controls [name, dosage form]

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified.

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 homogenizer) 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 3.2.P.3.4. 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 (3.2.P.3.3).

Additionally, for Biotech see Appendix 3.2.A.1 for facilities, if appropriate.

Reference ICH guidance Q6B.

3.2.P.3.4 Controls of Critical Steps and Intermediates [name, dosage form]

Critical Steps: Tests and acceptance criteria (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process should be provided 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 guidances Q2A, Q2B, Q6A, and Q6B.

3.2.P.3.5 Process Validation and/or Evaluation [name, dosage form]

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in Appendix 3.2.A.2, if necessary.

Reference ICH guidance Q6B.

3.2.P.4 Control of Excipients [name, dosage form]

3.2.P.4.1 Specifications [name, dosage form]

The specifications for excipients should be provided.

Reference ICH guidances Q6A and Q6B.

3.2.P.4.2 Analytical Procedures [name, dosage form]

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

Reference ICH guidances Q2A and Q6B.

3.2.P.4.3 Validation of Analytical Procedures [name, dosage form]

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

Reference ICH guidances Q2A, Q2B, and Q6B.

3.2.P.4.4 Justification of Specifications [name, dosage form]

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

Reference ICH guidances Q3C and Q6B.

3.2.P.4.5 Excipients of Human or Animal Origin [name, dosage form]

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data). (Provide details in Appendix 3.2.A.2).

Reference ICH guidances Q5A, Q5D, and Q6B.

3.2.P.4.6 Novel Excipients [name, dosage form]

For excipients used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross-references to supporting safety data (nonclinical and/or clinical), should be provided according to the drug substance format.

3.2.P. 5 Control of Drug Product [name, dosage form]

3.2.P.5.1 Specifications [name, dosage form]

The specifications for the drug product should be provided.

Reference ICH guidances Q3B, Q6A, and Q6B.

3.2.P.5.2 Analytical Procedures [name, dosage form]

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

Reference ICH guidances Q2A and Q6B.

3.2.P.5.3 Validation of Analytical Procedures [name, dosage form]

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

Reference ICH guidances Q2A, Q2B, and Q6B.

3.2.P.5.4 Batch Analyses [name, dosage form]

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

Reference ICH guidances Q3B, Q3C, Q6A, and Q6B.

3.2.P.5.5 Characterization of Impurities [name, dosage form]

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

Reference ICH guidances Q3B, Q5C, Q6A, and Q6B.

3.2.P.5.6 Justification of Specifications [name, dosage form]

Justification for the proposed drug product specifications should be provided.

Reference ICH guidances Q3B, Q6A, and Q6B.

3.2.P.6 Reference Standards or Materials [name, dosage form]

Information on the reference standards or reference materials used for testing of the drug product should be provided if not previously provided in 3.2.S.5, Reference Standards or Materials.

Reference ICH guidances Q6A and Q6B.

3.2.P.7 Container Closure System [name, dosage form]

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). Noncompendial methods (with validation) should be included where appropriate.

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

Suitability information should be located in 3.2.P.2.

3.2.P.8 Stability [name, dosage form]

3.2.P.8.1 Stability Summary and Conclusion [name, dosage form]

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

Reference ICH guidances Q1A, Q1B, Q3B, Q5C, and Q6A.

3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment [name, dosage form]

The postapproval stability protocol and stability commitment should be provided.

Reference ICH guidances Q1A and Q5C.

3.2.P.8.3 Stability Data [name, dosage form]

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

Information on characterization of impurities is located in 3.2.P.5.5.

Reference ICH guidances Q1A , Q1B, Q2A, Q2B, and Q5C.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

For Biotech:

A diagram should be provided illustrating the manufacturing flow, including movement of raw materials, personnel, waste, and intermediates 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, sterilization, 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.

3.2.A.2 Adventitious Agents Safety Evaluation

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

For nonviral adventitious agents:

Detailed information should be provided on the avoidance and control of nonviral 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 guidances 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.

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in 3.2.S.2.3, and 3.2.P.4.5). 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 3.2.S.2.3).

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk, or postviral 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 3.2.S.2.4 and 3.2.P.3.4). In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

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 3.2.S.2.5 and 3.2.P.3.5).

Reference ICH guidances Q5A, Q5D, and Q6B.

3.2.A.3 Novel Excipients

3.2.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 guidance 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)

3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.