POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Product Quality Microbiology Information in the Common Technical Document - Quality (CTD-Q)

Table of Contents

PURPOSE

- This MAPP will assist the product quality microbiology reviewer in the Center for Drug Evaluation and Research (CDER) by providing the expected locations of product quality microbiology information in applications submitted in the CTD-Q format.

BACKGROUND

- New drug application (NDA) or abbreviated new drug application (ANDA) submissions containing product quality microbiology information are usually formatted in a manner consistent with the organization of the guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. Pharmaceutical manufacturing firms may now submit applications using the CTD-Q, which is the common format agreed upon by the International Conference on Harmonisation (ICH). The CTD-Q format differs considerably from the previous format used by firms for submission of product quality microbiology information; therefore, reviewers need assistance on locating critical product quality microbiology information in applications submitted in the CTD-Q format.

PROCEDURES

1. When reviewing an NDA or ANDA received in the CTD-Q format, microbiology reviewers should refer to Attachment A, which lists the CTD-Q sections that apply to microbiology, for cross-references as listed below.

    -- References in brackets show the location of related information in the sterilization process validation guidance.

    -- References in parentheses in the "S" section (drug substance) of the CTD-Q show the location of the corresponding information in the "P" section (drug product) of the CTD-Q.

    -- A reference in parentheses in the "P" section of the CTD-Q refers to the ICH Q6A guidance.

2. Reviewers should refer to Attachment B, which is the table of contents of the sterilization process validation guidance, for cross-references to the CTD-Q.

REFERENCES

1. Guidance for industry, *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*

2. ICH guidance for industry, *M4Q: The CTD – Quality*

3. ICH guidance for industry, *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
5/24/2004	original	N/A
2/26/2014	N/A	Administrative changes
x/xx/2017	N/A	Administrative changes made to reflect organization changes from Office of Pharmaceutical Science to Office of Pharmaceutical Quality and to update MAPP format

Attachment A Table of Contents Showing Intended Location for Product Quality Microbiology Information in Applications Submitted in the CTD-Q Format

The following is an excerpt from the table of contents of the *Common Technical Document – Quality (CTD – Q)* that provides the intended location of product quality microbiology information in an NDA or ANDA submitted in the CTD-Q format. More detailed guidance on the specific information to be included in an NDA or ANDA can be found in this guidance for industry on *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. References to the guidance are italicized and enclosed in brackets. References to other places in the CTD-Q or to the ICH guidance on Q6A specifications appear in parentheses.

MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

Prescribing Information
The proposed package label and package insert

MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

(Review sections S.2 through S.6 ONLY if the drug substance is sterile or if other product quality microbiology issues are involved. The required process and validation information for a sterile drug substance is the same as for a sterile drug product. References to the corresponding drug product sections of the CTD-Q and a reference to the ICH Q6A appear in parentheses for your convenience.)

S.2 Manufacture

S.2.1 Manufacturers

Name, address and responsibility of each manufacturing and testing facility.

S.2.2 Description of the Manufacturing Process and Process Controls

Description of the manufacturing process for the drug substance, including sterilization processes, and any in-process controls (P.3.3).

S.2.5 Process Validation and/or Evaluation

Validation of sterilization processes for the drug substance. (P.3.5)

S.4 Control of Drug Substance

S.4.1 Specification

Microbiological specification for the drug substance. (P.5.1)

S.4.2 Analytical Procedures

Microbiological analytical procedures used to test the drug substance. (P.5.2)

S.4.3 Validation of Analytical Procedures

Validation of the microbiological analytical procedures. (P.5.3)

S.6 Container Closure System

Description of the container-closure system used for the drug substance and the validation of the container-closure integrity. (P.2.5 and P.7)

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

Description of the drug product composition and the container-closure system. *[II.A.1]*

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity. *[II.E.1-4; IV.G]*
- Preservative Effectiveness. *[V.B]*
- Justification for not having a microbial limit specification for a non-sterile drug product, drug substance or excipient (see ICH Q6A, decision trees #8 and #6).

P.3 Manufacture

P.3.1 Manufacturers

Name, address and responsibility of each manufacturing facility and testing site.

P.3.3 Description of the Manufacturing Process and Process Controls

Description of the manufacturing process for the drug product, including sterilization processes, and any in-process controls. The sterilization information will also include sterilization/depyrogenation of packaging components and equipment. The description of the manufacturing process may be in the form of a narrative and/or a flow chart.

Examples of information that should be included for some sterilization processes:

Terminal moist heat

- Autoclave process and performance specifications *[II.A.2-3]*

- Autoclave loading patterns *[II.A.4]*
- Methods and controls to monitor production cycles *[II.A.5]*
- Requalification of production autoclaves *[II.A.6]*
- Reprocessing *[II.A.7]*
- Environmental monitoring including product bioburden *[II.C.1-2; II.D]*

Ethylene Oxide

- Description of the sterilizer *[III.A.1]*
- Cycle parameters *[III.A.2]*
- Microbiological controls *[III.A.3]*

Radiation Sterilization

- Facility and process *[III.B.1]*
- Product packaging *[III.B.2]*

Aseptic Fill

- Building and facilities (floorplan, air quality, equipment locations) *[IV.A]*
- Overall manufacturing operation (Filtration, holding periods) *[IV.B.]*
- Sterilization/Depyrogenation of containers, closures, equipment and components *[IV.C; IV.C.1]*
- Environmental monitoring *[IV.F]*

P.3.5 Process Validation and/or Evaluation

Validation of the sterilization process(es). The information should address validation of packaging component and equipment sterilization/ depyrogenation, filters, and any terminal sterilization processes.

Examples of information that should be included for some sterilization processes:

Terminal moist heat

- Heat distribution and penetration *[II.B.1]*
- Thermal monitors *[II.B.2]*
- Effects of loading *[II.B.3]*
- Microbiological efficacy of the cycle *[II.C.5]*
- Identification and characterization of bioburden *[II.C.1]*
- Characterization of biological indicators *[II.C.3-4]*

Ethylene oxide

- Microbiological validation *[III.A.3]*

Radiation sterilization

- Mapping studies *[III.B.3]*
- Microbiological methods and controls *[III.B.4]*

Aseptic Fill

- Drug product solution filtration *[IV.B.1]*

- Sterilization/Depyrogenation of containers, closures, equipment and components *[IV.C.; IV.C.1]*
- Holding periods *[IV.B.2]*
- Media fill procedures and specification *[IV.D]*
- Actions concerning product when media fills fail *[IV.E]*

P.5 Control of Drug Product *[II.F-G; IV.H-I]*

P.5.1 Specifications

Release specifications for the drug product (e.g., sterility, endotoxin, microbial limits).

P.5.2 Analytical Procedures

Methods for product release tests (e.g, sterility, endotoxin, microbial limits).

P.5.3 Validation of Analytical Procedures

Summary of validation procedures and results for analytical procedures (e.g, sterility, endotoxin, microbial limits).

P.7 Container Closure System

Description of the drug product container closure system *[II.A.1]*

P.8 Stability *[II.E.5; III.A.4; III.B.5; V.A; V.C]*

P.8.1 Stability Summary and Conclusion

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Analytical procedures and testing schedule for maintenance of microbial product quality (e.g., container-closure integrity/sterility, endotoxin, microbial limits).

P.8.3 Stability Data

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

Description of the processes used to control for potential contamination with adventitious agents (e.g., TSEs, viruses). These processes may include assays to detect adventitious agents, actions taken to avoid them, as well as procedures to eliminate or inactivate them.

R REGIONAL INFORMATION

R Executed Batch Record *[IV.C.2]*

Attachment B

TABLE OF CONTENTS OF 1994 GUIDANCE FOR INDUSTRY *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*

The following is the table of contents for the 1994 guidance for industry, *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. Cross-references to the CTD-Q appear at the end of the line.