Guidance for Industry

M4: The CTD — Quality Questions and Answers/ Location Issues

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

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I. INTRODUCTION (1)

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). The guidance for industry issued in November 2000 on preparing the CTD was divided into four separate documents: (1) M4: Organization of the CTD, (2) M4: The CTD — Quality, (3) M4: The CTD — Efficacy, and (4) M4: The CTD — Safety. Since implementation of these guidances, a number of questions regarding the CTD documents have been submitted to the various ICH regions. The ICH has developed a process for responding to questions submitted to the ICH Web site. This guidance specifically addresses questions related to quality. Other question and answer (Q & A) guidances address general questions as well as questions related to safety and efficacy. The questions and answers provided here reflect the consensus of the ICH parties.

[1] This guidance was developed within the M4 CTD-Quality Implementation Working Group 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 has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, July 18, 2003. 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.

Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process.

This document is intended to provide additional guidance for the preparation of an application file in the CTD-Q format (see section II: General Issues). It should be read in conjunction with the CTD-Q guidance (Modules 2 and 3). The document also addresses the relationship between linked CTD-Q sections for certain parameters, such as polymorphism, impurities, or particle size (see section III: Associated Information Located in Different Sections). This document also clarifies location issues; that is, it indicates in which CTD-Q section(s), requested information should be placed (see section IV: Location Issues in Drug Substance, section V: Location Issues in Drug Product, and section VI: Location Issues in Appendices).

This document does not address the content of an application file. For content questions, refer to the appropriate FDA guidance documents on this matter.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. GENERAL ISSUES (2)

A. Separate or Repeated Sections (2.1)

There can be a number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the CTD-Q heading, for example, 2.3.S Drug Substance (Name, Manufacturer A).

Drug Substance

When more than one drug substance is used in a drug product, information should be presented separately as one complete Drug Substance section followed by other complete Drug Substance sections. In some cases, for a single drug substance, it could be considered appropriate and logical to have information presented in multiple Drug Substance sections. For example, separate sections can be warranted when a single drug substance is made at two different manufacturing sites with differences in the manufacturing processes. However, despite these differences, it is likely that these different processes will be described within the same relevant subsection of 3.2.S. If, on the other hand, the differences result in, for example, different specifications, then adding an additional Drug Substance section is recommended (see also regional guidance).

Drug Product

Depending upon regional requirements, different drug product presentations (e.g., strengths, container closure types and configurations, formulations) and/or manufacturing schemes (e.g.,

aseptic and terminal sterilization) can be submitted in the same application. In general, when a single application can be submitted, information for each of the product presentations and manufacturing schemes should be combined and presented together in one Drug Product section, with information for each of the product presentations and manufacturing schemes provided in the Appendices and Regional Information sections, as warranted. For example, if 100 milligram (mg) tablets will be marketed in a bottle and a unit-dose blister package, the information should be presented in one Drug Product section. Where most of the quality information would be identical for the two drug products, the data common to both presentations should appear only once. The information that differs between the two should be presented as separate documents under the appropriate subsections (e.g., 3.2.P.7 Container Closure System, 3.2.P.8 Stability).

In some cases, however, for product presentations or manufacturing schemes that can be included in a single application, it is considered more appropriate and logical to have information presented separately. Information presented separately means one complete Drug Product section followed by other complete Drug Product sections. One such example is that information on a drug product supplied with a reconstitution diluent should be presented in separate Drug Product sections for the drug product and the reconstitution diluent. These could be titled 3.2.P (Drug Product) and 3.2.P (Diluent).

Excipients

If appropriate, where a novel, or noncompendial nonnovel, excipient is proposed and a significant amount of data is provided for the excipient, this information should be provided in 3.2.A.3 Excipients, which follows the same format and level of subsections as the Drug Substance section. There should be a complete section of 3.2.A.3 Excipients for each novel excipient or noncompendial nonnovel excipient.

Appendices

There can be occasions where it is appropriate to repeat an Appendix. For example, where a sponsor registers more than one manufacturing facility for the manufacture of a *biotech* drug, the Appendix 3.2.A.1 should then be repeated.

Regional Information

The content of the Regional Information section (3.2.R) is not harmonized. In this section the documents, their titling, and their order should be consistent with the requirements of the relevant region.

B. Multiple Containers (2.2)

When there are two containers (e.g., PVC blister and PE bottle) for one drug product, the documents for the drug product part in Module 3 should generally be common. In this case, one set of documentation, 3.2.P.1 through 3.2.P.8, should be provided. The information for the blister and the bottle should be presented in the corresponding sections of the single drug product

part in Module 3 (e.g., 3.2.P.7, 3.2.P.8), divided by subsections for each type of container and identified by the type of container.

C. Bioanalytical Methods (2.3)

Q: In the Common Technical Document, under what section should bioanalytical methods and their associated validation reports be included?

A: In this context, bioanalytical methods are understood to mean analytical procedures used in clinical studies (human clinical pharmacology/bioavailability/bioequivalence) and/or nonclinical studies (nonhuman pharm/tox studies).

The description of analytical procedures and associated validation reports should be submitted in those modules where the corresponding studies are described (i.e., in Module 4, section 4.2.2.1 for analytical procedures and associated validation reports for nonclinical studies and in Module 5, section 5.3.1.4 for analytical procedures and associated validation reports used in clinical studies).

D. Drug Master Files (DMFs) (2.4)

Q: Can the Drug Master File use the CTD format?

A: Since the DMF systems differ in the three regions, ICH does not address this issue. Consequently, the applicant should check with the relevant competent authority in the region(s).

E. Drug Substance Containing Additives (2.5)

Q: If a drug substance is used in the form of a preparation (e.g. a [commercially available] vitamin trituration) in which module/section should the excipient(s) included in the preparation be described? Should the relevant information be given for example in Section 3.2.S Drug Substance or in Section 3.2.P.4 Drug Product - Control of Excipients?

A: If the drug substance is defined as two or more materials, the manufacturing information would be described in 3.2.S.2.2 and the control of the additional material(s) (e.g., excipient(s)) would be described in 3.2.S.2.3.

III. ASSOCIATED INFORMATION LOCATED IN DIFFERENT SECTIONS (3)

Below, examples of multiple references in CTD-Q are proposed for polymorphism, particle size, and impurities. They indicate for some parameters that the information should not necessarily be located in one section, but should be split into different sections.

A. Polymorphism (3.1)

3.2.S.1.3 If called for, list the polymorphic form(s) present in the proposed active as a characteristic of the drug substance.

3.2.S.2.2 Description of Manufacturing Process and Process Controls should indicate which polymorphic form is synthesized.

3.2.S.3.1 Studies performed to identify the potential polymorphic forms of the drug substance, including study results. Total number of polymorphs should be listed here and those intended to form the active should be summarized in 3.2.S.1.3.

3.2.S.4.1 Specification. If a polymorph is to be defined or limited, it should be discussed here.

3.2.S.4.2 Analytical Procedures.

3.2.S.4.3 Validation of Analytical Procedures.

3.2.S.4.4 Results of batch analyses.

3.2.S.4.5 Justification of Specification (if appropriate). Reasons why a particular limit on form is appropriate (should also probably refer to 3.2.P.2).

3.2.P.2.1.1 and 3.2.P.2.2.3 Identifies the influence of polymorphism on the drug substance and dosage form.

3.2.P.5.1 Specification. If polymorphs are to be controlled in the drug product, they should appear here.

3.2.P.5.6 Justification of Specification (if called for).

B. Particle Size (3.2)

3.2.S.2.2 Description of Manufacturing Process and Process Controls.

3.2.S.3.1 Studies performed to identify the particle size distribution of the drug substance.

3.2.S.4.1 Specification.

3.2.S.4.2 Analytical Procedures.

3.2.S.4.3 Validation of Analytical Procedures.

3.2.S.4.4 Results of batch analyses.

3.2.S.4.5 Justification of Specification.

3.2.P.2.1.1 and 3.2.P.2.2.1 Identification of the influence of particle size on, for instance, dissolution performance (consult the ICH Q6A decision tree).

C. Impurities (3.3)

3.2.S.3.2 Here the discussion on impurities and information on their qualification should take place (reference to preclinical and clinical studies): e.g., absolute amount at which the impurities can be considered as qualified.

3.2.S.4.1 Specification.

3.2.S.4.2 Analytical Procedures.

3.2.S.4.3 Validation of Analytical Procedures.
3.2.S.4.4 Results of batch analyses (all batches including development, clinical, stability).
3.2.S.4.5 Justification of Specification.

3.2.P.5.1 Specification.
3.2.P.5.2 Analytical Procedures.
3.2.P.5.3 Validation of Analytical Procedures.
3.2.P.5.4 Results of batch analyses (all batches including development, clinical, stability).
3.2.P.5.5 Characterization of Impurities (for those impurities not already discussed under 3.2.S).
3.2.P.5.6 Justification of Specification.

D. New Location of Quality Information for Investigational Formulations (3.4)

Q: How does the CTD link information on drug substance batch numbers, drug product batch numbers, nonclinical and clinical study numbers, the levels of impurities, history of formulation development, and any other relevant information? Please clarify the assignment of this information to the nonclinical and clinical sections.

A: The history of development for the drug substance should be included in 3.2.S.2.6. A description of batches and the result of batch analyses should be included in 3.2.S.4.4. The history of formulation development should be included in 3.2.P.2.2.1. A description (including a summary table) of batches and the results of batch analyses for the drug product should be included in 3.2.P.5.4. This information on the history of development and description of batches can also be linked to the impurity levels of batches described in 3.2.S.3.2 and 3.2.P.5.5.

Appropriate references to Modules 4 and 5 for the nonclinical and clinical studies can also be made.

E. Information Related to Nonviral Adventitious Agents (3.5)

Q. Where would the information related to nonviral adventitious agents be placed within Module 3.2?

A: The following guidance supersedes the first sentence under 3.2.A.2 for nonviral adventitious agents:

The detailed information regarding the routine manufacturing control of adventitious agents, such as bacteria, mycoplasma, and fungi, typically using well-established (e.g., pharmacopoeial) analytical procedures, should be provided in the appropriate sections within Module 3.2.S and 3.2.P. If well-established (e.g., pharmacopoeial) analytical

procedures are not used, more detailed information regarding the analytical procedure(s) used should also be included in 3.2.S and 3.2.P.

With respect to other nonviral adventitious agents, such as transmissible spongiform encephalopathy agents and prions, the detailed information, should be placed in 3.2.A.2.

IV. LOCATION ISSUES IN DRUG SUBSTANCE: 3.2.S (4)

CTD-Q Section 3.2.

S.1 General Information

S.1.1 Nomenclature
S 1.2 Structure

Q: Should drawings to show secondary and tertiary structures and, if applicable, quaternary structures of proteins be provided in 3.2.S.1.2?

A: Drawings to show secondary and tertiary structures and, if applicable, quaternary structures should be provided in 3.2.S.3.1.

S.1.3 General Properties

Q: How much detailed information on the general properties of the drug substance should be included in 3.2.S.1.3?

A: As stated in CTD-Q, a list of physicochemical and other relevant properties of the drug substance, including biological activity, should be included in 3.2.S.1.3. The information on general properties should be provided only for the form of the drug substance used in the drug product, not possible alternative forms (e.g., polymorphs). More detailed information on the properties of the drug substance, including possible alternative forms, should be included in 3.2.S.3.1.

S.2 Manufacture

S.2.1 Manufacturers
S.2.2 Description of the Manufacturing Process and Process Controls

Q: Should information on process controls be provided in section 3.2.S.2.2 or 3.2.S.2.4?

A: All process controls should be identified in 3.2.S.2.2. For critical controls, additional information should be provided in 3.2.S.2.4.

S.2.3 Control of Materials

Q1: Should the discussion and justification of starting materials be included in 3.2.S.2.3?

A1: The discussion and justification of starting materials should be included in 3.2.S.2.3.

Q2: Where should analytical procedures for materials described in 3.2.S.2.3 be included?

A2: The analytical procedures for the control of materials (e.g., starting materials, reagents, raw materials, solvents) should be presented in section 3.2.S.2.3. For materials of biological origin, analytical procedures related to adventitious agent safety evaluation, if applicable, should be presented in 3.2.A.2.

Q3: Since the addition of new headings is not an option, where in the CTD should one locate (Quality Section) information regarding a reagent used in the production of the drug substance when the reagent is manufactured via recombinant DNA technology?

A3: The information should be located in 3.2.S.2.3: Control of Materials.

S.2.4 Control of Critical Steps and Intermediates

Q1: Should batch data for intermediates or critical steps be included in 3.2.S.2.4?

A1: Batch data, together with analytical procedures and acceptance criteria for intermediates or critical steps, would be presented in 3.2.S.2.4.

Q2: If release tests are performed on intermediates and at critical steps instead of on drug substance, where would the information on the analytical procedures and acceptance criteria be presented in 3.2.S.4?

A2: Acceptance criteria should be referred to in 3.2.S.4.1, and analytical procedures should be referred to in 3.2.S.4.2.

S.2.5 Process Validation and/or Evaluation

Q: Where should justification for reprocessing be included?

A: If justification for reprocessing is warranted by a regional authority, the information would be included as part of the description of the manufacturing process in 3.2.S.2.2. If there are critical controls associated with the reprocessing operation, the critical controls should be included in 3.2.S.2.4. If validation information is warranted, the validation information should be included in 3.2.S.2.5.

S.2.6 Manufacturing Process Development

Q: Should bioavailability/bioequivalence study results that demonstrate product comparability following process changes be described in 3.2.S.2.6?

A: Reports of Bioavailability/Bioequivalence studies that demonstrate comparability/equivalence after formulation or process changes should be presented in

Module 5. Cross-references to these reports should be placed in section 3.2.S.2.6 (for drug substance process changes), 3.2.P.2.2.1 (for drug product formulation changes) or 3.2.P.2.3 (for drug product process changes). A brief summary of the reports can be placed in these sections when considered appropriate.

S.3 Characterization

S.3.1 Elucidation of Structure and Other Characteristics

Q: Where should studies conducted to determine the physicochemical characteristics of the drug substance be included?

A: Information on the studies conducted to determine the physicochemical characteristics of the drug substance should be included in 3.2.S.3.1. Only a list of the general properties of the drug substance should be included in 3.2.S.1.3.

S.3.2 Impurities

Q1: Should structural characterization data and a summary of the method of preparation of impurities be included in 3.2.S.3.2?

A1: This information should be included in 3.2.S.3.2. Characterization of impurity reference standards should be provided in 3.2.S.5. See also Q & A under III.C.

Q2: Where should chromatograms be provided for impurities?

A2: ICH Q3A identifies the chromatograms as part of the analytical validation studies. Therefore, relevant chromatograms should be included in 3.2.S.4.3.

Q3: Where should nonclinical and clinical data supporting impurity levels be summarized?

A3: The qualified level of each impurity with cross-reference to the supporting nonclinical/clinical studies should be included in 3.2.S.3.2.

Q4: Should data on impurities reported in batch analyses be included in 3.2.S.3.2 or 3.2.S.4.4?

A4: Data on observed impurities for relevant batches (e.g., clinical, nonclinical, stability) should be provided in 3.2.S.3.2. The data should be provided whether or not the impurity is included in the specification. This information can be cross-referenced to support other sections of the application as appropriate.

S.4 Control of Drug Substance

S.4.1 Specification

Q1: If there are different specifications for a drug substance manufacturer and/or applicant, should they all be provided in 3.2.S.4.1?

A1: When appropriate, more than one specification should be included in 3.2.S.4.1.

Q2: If alternative analytical procedures are used to control the drug substance, should they also be listed in the specification (3.2.S.4.1)?

A2: Any analytical procedure used to control the drug substance, and the associated acceptance criteria, should be listed in the specification.

S.4.2 Analytical Procedures

Q1: Often an analytical procedure changes during the development of the drug substance. If this analytical procedure is submitted to support the dossier, in which section should these analytical procedures be placed?

A1: Information on historical analytical procedures used to generate data included in the batch analyses should be included in 3.2.S.4.4.

Q2: Should an analytical procedure that is only used for stability studies be included in 3.2.S.4.2?

A2: Information on analytical procedures that are used only for stability studies should be included in 3.2.S.7.3.

Q3: If the analytical methods for a drug substance and drug product are identical, can these methods and corresponding validation, if applicable, be described in either 3.2.S or 3.2.P, with a corresponding reference (e.g., a reference from 3.2.S to 3.2.P)?

A3: The analytical methods should be placed in both the relevant sections of 3.2.S and 3.2.P because the sample preparation, at least, will differ.

S.4.3 Validation of Analytical Procedures

Q: Where should chromatograms be included?

A: Relevant chromatograms should be included in 3.2.S.4.3.

S.4.4 Batch Analyses

Q1: Where should results from all relevant batches be provided?

A1: Results from all relevant batches (e.g., clinical, nonclinical, stability), including those batches used to justify acceptance criteria should be provided in 3.2.S.4.4.

Q2: If there are results from tests that are not listed in the specifications, where should they be provided?

A2: If results are submitted from tests that are not listed in the specification, they should be provided in 3.2.S.4.

Q3: Where should collated data for a test from multiple batch analyses be presented?

A3: If collated data from batch analyses are warranted, the data should be presented in 3.2.S.4.4.

S.4.5 Justification of Specification

Q1: Should justification for skip testing be included in 3.2.S.4.5?

A1: If skip testing is considered appropriate, the justification should be included in 3.2.S.4.5.

Q2: Rather than repeating information, can a summary of data from other sections with a cross-reference to the detailed information be provided to support the justification of specification section of the dossier?

A2: A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.

S.5 Reference Standards or Materials

Q1: Reference standards might be available for the active moiety and impurities. Should information on all reference standards be included in 3.2.S.5?

A1: If information is warranted for a reference standard, the information should be included in 3.2.S.5.

Q2: Where should characterization data for a reference standard be placed in the CTD-Q?

A2: Characterization data for the reference standard should be included in 3.2.S.5. Cross-reference to information in other sections (e.g., 3.2.S.3.2) can be included as considered appropriate.

S.6 Container Closure System

S.7 Stability

S.7.1 Stability Summary and Conclusions
S.7.2 Postapproval Stability Protocol and Stability Commitment
S.7.3 Stability Data

Q1: Should stress studies be located in 3.2.S.7.3?

A1: Stress studies should be located in 3.2.S.7.3. These data can be referenced for validation of analytical procedures as considered appropriate.

Q2: Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.S.7.3?

A2: Information on historical analytical procedures used to generate the stability data should be included in 3.2.S.7.3.

Q3: Can data from supporting studies be included in 3.2.S.7.3?

A3: Data from supporting studies can be included in 3.2.S.7.3, if considered appropriate.

Q4: Should information on analytical procedures unique to the stability program be presented in 3.2.S.7.3?

A4: Information on analytical procedures unique to the stability program should be included in 3.2.S.7.3.

V. LOCATION ISSUES IN DRUG PRODUCT: 3.2.P (5)

CTD-Q Section 3.2

P.1 Description and Composition of the Drug Product

Q1: Where should information related to the composition of inks used on the drug product be placed?

A1: All drug product components should be listed in 3.2.P.1. The composition (e.g., components of the capsule shell, components of inks) should also be included in 3.2.P.1. In some regions, the qualitative composition of proprietary components can be replaced with reference to appropriate DMFs.

Q2: Where should information on reconstitution diluents be included?

A2: If the diluent is co-packaged with the drug product, the information on the diluent should be placed in a separate Drug Product section. The compatibility of the drug product with reconstitution diluents should be discussed in 3.2.P.2.6.

Q3: Should an over-fill be indicated in 3.2.P.1?

A3: The use of an over-fill should be indicated in 3.2.P.1. The rationale for an overfill should be included in 3.2.P.2.2.1.

Q4: Can information on the composition of a drug product, other than what is listed in the CTD-Q guidance, be included in 3.2.P.1?

A4: When called for, additional information can be included to adequately describe the composition of the drug product, for example, (1) total weight, volume, etc., of unit, (2) tracers or markers, (3) composition statement for (purchased) mixtures, and (4) capsule shells.

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product

Q1: Where should information on the development of co-packaged diluents be placed?

A1: There should be a separate Drug Product (Diluent) section for co-packaged diluents. Choice and development of co-packaged diluents should be included in 3.2.P.2.2.1 and 3.2.P.2.6.

P.2.1.1 Drug Substance

Q1: Where should a discussion of the drug substance stability or key physicochemical characteristics that might influence the manufacturing process of the drug product be provided?

A1: Drug substance stability data should be included in 3.2.S.7 and cross-referenced as needed in 3.2.P.2 as appropriate. Discussion of key drug substance physicochemical characteristics that can influence manufacturability of the drug product should be included in 3.2.P.2.1.1.

Q2: Where should a discussion of the effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics be provided?

A2: Discussion of effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics should be included in 3.2.P.2.1.1.

Q3: Where should data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics be provided?

A3: Data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics should be provided in 3.2.P.2.1.1 (see ICH Q6A Decision Trees 3 and 4 (Part 2)).

P.2.1.2 Excipients

Q1: Should justification for using an excipient if there is evidence of incompatibility be included in 3.2.P.2.1.1 or 3.2.P.2.1.2?

A1: Justification for using an excipient if there is evidence of incompatibility should be included in 3.2.P.2.1.1.

Q2: Where should a discussion of an excipient's influence on the manufacturability of the drug product be included?

A2: Discussion of excipients that can influence the manufacturability of the drug product should be included in 3.2.P.2.1.2.

Q3: Where should a discussion of the ability of a functional excipient to perform through shelf-life be included?

A3: Discussion of the ability of functional excipients (e.g., antioxidants, penetration enhancers) to perform through shelf-life should be included in 3.2.P.2.1.2. The effectiveness of antimicrobial preservatives should be discussed in 3.2.P.2.5.

P.2.2 Drug Product

Q: Where should tables that describe the composition of formulations used in development studies be included?

A: Tables describing different development formulations should be included in 3.2.P.2.2.1.

P.2.2.1 Formulation Development

Q1: Where should information on IV-IV correlation be included in CTD-Q?

A1: Summarized information on the in vivo-in vitro (IV-IV) correlation should be included in 3.2.P.2.2.1 with a cross-reference to the studies in Module 5.

Q2: Can cross-reference be made to bioequivalence information in other modules?

A2: Cross-referencing to both Modules 2 and 5 can be included to facilitate the review process.

Q3: Where should information to justify a scoring of tablets be included?

A3: The rationale/justification for scoring of tablets should be provided in 3.2.P.2.2.1.

Q4: Should the release mechanism of the dosage form for controlled release drug products be described in 3.2.P.2.2.1?

A4: Description of the release mechanism in the dosage form for controlled release drug products should be included in 3.2.P.2.2.1.

P.2.2.2 Overages

Q: Where should overages be justified?

A: Justification for overages should be included in 3.2.P.2.2.2.

P.2.2.3 Physicochemical and Biological Properties

Q1: Where should any discussion on dissolution development be included?

A1: A summary of dissolution development should be included in 3.2.P.2.2.3, with cross-reference to studies in Module 5, as considered appropriate. The justification for the dissolution test should be included in 3.2.P.5.6.

Q2: Where should a discussion of the key drug product physicochemical or biological characteristics that might influence the manufacturing process of the drug product be provided?

A2: A discussion of key drug product physicochemical or biological characteristics that can influence manufacturability of the drug product should be included in 3.2.P.2.2.3.

Q3: Where should data from studies on the potential effects of key drug substance physiochemical characteristics on the performance of the drug product be provided?

A3: Data from studies on drug product to evaluate the appropriateness of the drug product acceptance criteria for physicochemical/biological properties should be included in 3.2.P.2.2.3 (see ICH Q6A Decision Trees 4 (Part 3) and 7 (Part 1)).

P.2.3 Manufacturing Process Development

Q1: Where should justification of sterilization be provided?

A1: When called for, justification of sterilization should be included in 3.2.P.2.3.

Q2: What information on clinical trial formulations should be included in 3.2.P.2.3?

A2: Information on clinical trial formulations should be included in 3.2.P.2.2.1. Information on the differences in the manufacturing process among supporting batches (e.g., clinical, stability) and the proposed production process should be included in 3.2.P.2.3.

P.2.4 Container Closure System

Q1: Should information on container closure system leachables and extractables be included in 3.2.P.2.4?

A1: Information on both should be included in 3.2.P.2.4. When warranted, information on leachables should also be included in 3.2.P.5.1 and 3.2.P.5.5. Also, if leachables are confirmed through shelf-life as part of the formal stability studies, the results would be reported in 3.2.P.8.3.

Q2: Where should performance characteristics of a container closure be provided?

A2: Information on performance of the container closure system should be included in 3.2.P.2.4 (e.g., priming and re-priming studies for metered dose inhalers).

Q3: Where should information on studies relating to cleaning of metered dose inhalers be included?

A3: Information on cleaning of metered dose inhalers should be included in 3.2.P.2.4.

Q4: Where should information on the light protection characteristics of the container closure be provided?

A4: Suitability of the container closure system to protect from light (e.g., light transmission data) should be discussed in 3.2.P.2.4. Photostability data should be provided in 3.2.P.8.3 (defined as a stress study in Q1A/Q1B).

P.2.5 Microbiological Attributes

Q: Should discussion of Decision Tree #6 from ICH Q6A be included in 3.2.P.2.5?

A: Discussions relating to ICH Q6A Decision Tree #6 (nonsterile drug substance and excipients) and Decision Tree #8 (nonsterile solid) should be provided in 3.2.P.2.5.

P.2.6 Compatibility

Q1: Where should data from constitution or dilution studies performed as part of the formal stability studies to confirm product quality through shelf-life be provided?

A1: Information on the compatibility of reconstitution diluents to support claims on the label should be included in 3.2.P.2.6. Data from constitution or dilution studies that are performed as part of the formal stability studies to confirm product quality through shelf-life should be reported in 3.2.P.8.3.

Q2: Should compatibility of co-administered drugs be provided in 3.2.P.2.6?

A2: Compatibility with co-administered drugs should be included in 3.2.P.2.6.

Q3: Should information on incompatible diluents be provided in 3.2.P.2.6?

A3: Information on incompatible diluents should be provided in 3.2.P.2.6.

P.3 Manufacture

P.3.1 Manufacturer(s)
P.3.2 Batch Formula

Q: Should overages be included in 3.2.P.3.2?

A: Overages should be included in the batch fomula in 3.2.P.3.2.

P.3.3 Description of Manufacturing Process and Process Controls

Q1: Where should reprocessing be described?

A1: Reprocessing should be included as part of the description of the manufacturing process in 3.2.P.3.3. If there are critical controls associated with the reprocessing operation, the critical controls should be included in 3.2.P.3.4. If validation information is warranted, the validation information should be included in 3.2.P.3.5.

Q2: Should critical steps and intermediates be identified in P.3.3?

A2: All process controls should be identified in 3.2.P.3.3. For critical controls, additional information should be provided in 3.2.P.3.4.

Q3: Should an over-fill be identified in 3.2.P.3.3?

A3: An over-fill should be identified in 3.2.P.3.3.

Q4: Should a statement regarding manipulation of ruminant-derived materials in the drug product manufacturing facility be included in 3.2.P.3.3?

A4: A statement regarding manipulation of ruminant-derived materials in the drug product manufacturing facility should be included here (3.2.P.3.3). If a potential for cross-contamination with adventitious agents exists, additional information should be provided in 3.2.A.1 and 3.2.A.2.

P.3.4 Controls of Critical Steps and Intermediates

Q1: Should the detailed information on critical steps and intermediates that have been identified in 3.2.P.3.3 be included in 3.2.P.3.4?

A1: Detailed information should be provided in 3.2.P.3.4 for critical steps and all intermediates that are controlled.

Q2: Should critical process control values from relevant batches be included in 3.2.P.3.4 to support numeric ranges, limits, etc., for the critical process controls?

A2: Critical process control values from relevant batches to support numeric ranges, limits, etc., for critical process controls should be included in 3.2.P.3.4.

Q3: Where should information on the analytical procedures for an in-process material test performed in lieu of a finished product test be included?

A3: In 3.2.P.3.4, the same information should be provided for an in-process material test performed in lieu of a finished product test as that submitted for a finished product test (analytical procedure, methods validation information).

Q4: If a process test were to replace an end-product test, where would it be mentioned in the specification?

A4: If a process test takes the place of an end-product test, it should be listed in the specification (3.2.P.5.1) and specified as a process test (see ICH Q6A).

P.3.5 Process Validation and/or Evaluation

P.4 Control of Excipients

Q: If a significant amount of data for an excipient (e.g., a novel excipient or a noncompendial nonnovel excipient) needs to be provided, where would it be placed?

A: This information should be included in 3.2.A.3 Excipients, if required. If only a minimal amount of information was necessary for these excipients (e.g., pharmacopoeial), this information should be provided in 3.2.P.4.1 and/or 3.2.P.2.1.2.

P.4.1 Specifications
P.4.2 Analytical Procedures
P.4.3 Validation of Analytical Procedures
P.4.4 Justification of Specifications

Q1: Where should certificates of analysis or batch data for excipients be included?

A1: Certificates of analysis or batch data for excipients should be included in 3.2.P.4.4.

Q2: Can a summary of data from other sections with a cross-reference to the detailed information be provided, rather than repeating this information to support the Justification of Specifications section of the dossier?

A2: A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.

P.4.5 Excipients of Human or Animal Origin

Q: Where should information on excipients of human or animal origin be located?

A: Information on excipients of human or animal origin should be included in 3.2.P.4.5. Information on adventitious agent safety evaluation should be included in 3.2.A.2. For the location of certifications relating to TSE/BSE, see region specific guidance.

P.4.6 Novel Excipients

P.5 Control of Drug Product

P.5.1 Specification(s)

Q1: Where should release and shelf-life specifications be located?

A1: Both specifications should be included in 3.2.P.5.1. (See also question for 3.2.P.8.1)

Q2: If alternative analytical procedures are used to control the drug product, should they be listed in the specification (3.2.P.5.1) also?

A2: Any analytical procedure used to control the drug product, and the associated acceptance criteria, should be listed in the specification.

P.5.2 Analytical Procedures

Q1: Often an analytical procedure changes during the development of the drug product. If this analytical procedure is submitted to support the dossier, in which section should it be placed?

A1: Information on historical analytical procedures used to generate data included in the Batch Analyses section should be included in 3.2.P.5.4.

Q2: Should an analytical procedure that is only used for stability studies be included in 3.2.P.5.2?

A2: Information on analytical procedures that are used only for stability studies should be included in 3.2.P.8.3.

Q3: If the analytical methods for a drug substance and drug product are identical, can these methods and corresponding validation, if applicable, be described in either 3.2.S or 3.2.P, with a corresponding reference (e.g., a reference from 3.2.S to 3.2.P)?

A3: The analytical methods should be placed in both the relevant sections of 3.2.S and 3.2.P because the sample preparation, at least, will usually differ.

P.5.3 Validation of Analytical Procedures
P.5.4 Batch Analyses

Q1: Should results from all batches be provided in 3.2.P.5.4? Should the description of the batches (e.g., batch number, manufacturing site, use) be included in 3.2.P.5.4?

A1: Results from all relevant batches (e.g., clinical, nonclinical, stability), including those batches used to justify acceptance criteria, should be provided in 3.2.P.5.4. Information describing the batches should also be included in 3.2.P.5.4.

Q2: If there are results from tests that are not listed in the specifications, where should they be provided?

A2: If results are submitted from tests that are not listed in the specification, they should be provided in 3.2.P.5.4.

Q3: Where should collated data for a test from multiple batch analyses be presented?

A3: If collated data from batch analyses are warranted, the data should be presented in 3.2.P.5.4.

P.5.5 Characterization of Impurities

Q1: Should all observed impurities be listed in 3.2.P.5.5 even if they are not included in the drug product specification?

A1: All observed impurities should be listed. Justification for not including an observed impurity in the specification should be included in 3.2.P.5.6.

P.5.6 Justification of Specification(s)

Q1: Should justification for skip testing be included in 3.2.P.5.6?

A1: If skip testing is considered appropriate, the justification should be included in 3.2.P.5.6.

Q2: Can a summary of data from other sections with a cross-reference to the detailed information be provided to support the justification of the specification rather than repeating information?

A2: A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.

P.6 Reference Standards or Materials

Q: Reference standards might be available for the active moiety and impurities. Should information on all reference standards be included in 3.2.P.6?

A: Where considered appropriate, a reference standard cited in 3.2.S.5 can be cross-referenced in 3.2.P.6. Information on all other reference standards should be included in 3.2.P.6.

P.7 Container Closure System

P.8 Stability

P.8.1 Stability Summary and Conclusion

Q1: Should the shelf-life specification be repeated under this section?

A1: The shelf-life specification should be indicated in 3.2.P.8.1.

Q2: Where should the design and justification for a reduced stability design (e.g., bracketing or matrixing) be discussed?

A2: The design and justification for a reduced stability design should be included in 3.2.P.8.3.

P.8.2 Postapproval Stability Protocol and Stability Commitment

P.8.3 Stability Data

Q1: Should stress studies be located in 3.2.P.8.3?

A1: Stress studies should be located in 3.2.P.8.3. These data can be referenced for validation of analytical procedures as considered appropriate.

Q2: Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.P.8.3?

A2: Information on historical analytical procedures used to generate the stability data should also be included in 3.2.P.8.3.

Q3: Can data from supporting studies be included in 3.2.P.8.3?

A3: Data from supporting studies can be included in 3.2.P.8.3, if considered appropriate.

Q4: Should information on analytical procedures unique to the stability program be presented in 3.2.P.8.3?

Information on analytical procedures unique to the stability program should be included in 3.2.P.8.3

Q5: Where should the statistical analysis of the stability data be included?

A5: The detailed statistical analysis report, if included, should go in 3.2.P.8.3, and a summary or conclusions of the statistical analysis should go in 3.2.P.8.1.

VI. LOCATION ISSUES IN APPENDICES: 3.2.A (6)

CTD-Q Section 3.2.

A. Appendices

Q1: If information for both the drug substance and the drug product should be included in an appendix (e.g., 3.2.A.1), how should it be presented?

A1: If drug substance and drug product information is included in the appendices, then the preferred presentation is drug substance first and then drug product within each section, for example, 3.2.A.1 (Drug Substance, then Drug Product), then 3.2.A.2 (Drug Substance, then Drug Product), then 3.2.A.3 (Drug Substance, if applicable, then Drug Product).

Q2: Should 3.2.A.3 be retitled from Novel Excipients to Excipients to include noncompendial, nonnovel excipients?

A2: At ICH, the title of 3.2.A.3 was changed to Excipients (see 3.2.P.4) to include noncompendial nonnovel excipients.