Common Technical Document – Quality

Questions and Answers / Location Issues

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Table of Contents

1. Introduction

This document is intended to give additional guidance for the preparation of an application file in the CTD-Q format in the applicable regions. (See under 2. General Issues.) It should be read in conjunction with the CTD-Q (Modules 2 and 3). It also addresses the relationship between linked sections for certain parameters like polymorphism, particle size, etc. (See under 3. Multiple links between different sections.) This document also clarifies location issues i.e. it indicates, when information is requested, in which section it should be addressed. (See under 4. Location Issues in Drug Substance and under 5. Location Issues in Drug Product.)

This document does not address the content of an application file. Refer to regional guidances.

2. General Issues

2.1 Definition of a Quality Document

In deciding whether one or more documents or files are appropriate, it should be considered that once a particular approach has been adopted, the same approach should be used throughout the life of the dossier.

Quality documents in either the paper or electronic dossier are defined as follows:

Module 2:

A separate document should be provided for 2.3 Quality Overall Summary Introduction.

For the following sections of the Quality Overall Summary, the applicant can has the option to either submit one document with multiple subheadings and subsection numbering, as defined in the M4Q guidance:

- 2.3.S Drug Substance
- 2.3.P Drug Product
- 2.3.A Appendices

or submit one document for each of the defined subheadings and subsections, as follows: e.g.

- 2.3.S.1 General Information
- 2.3.S.2 Manufacture
- 2.3.S.3 Characterization
- 2.3.S.4 Control of Drug Substance
- 2.3.S.5 Reference Standards or Materials
- 2.3.S.6 Container Closure System
- 2.3.S.7 Stability

- 2.3.P.1 Description and Composition of the Drug Product
- 2.3.P.2 Pharmaceutical Development

2.3.P.3 Manufacture
2.3.P.4 Control of Excipients
2.3.P.5 Control of Drug Product
2.3.P.6 Reference Standards or Materials
2.3.P.7 Container Closure System
2.3.P.8 Stability

2.3.A.1 Facilities and Equipment
2.3.A.2 Adventitious Agents Safety Evaluation
2.3.A.3 Excipients

Similarly, the applicant has the option to submit one document or multiple documents i.e. one document for each subsection, as defined according to the appropriate regional guidance(s), under 2.3.R Regional Information.

Module 3:

A separate document should be provided for each of the following sections:

3.2.S.1.1 Nomenclature
3.2.S.1.2 Structure
3.2.S.1.3 General Properties
3.2.S.2.1 Manufacturer(s)
3.2.S.2.2 Description of Manufacturing Process and Process Controls
3.2.S.3.1 Elucidation of Structure and Other Characteristics
3.2.S.3.2 Impurities
3.2.S.4.1 Specification
3.2.S.4.4 Batch Analyses
3.2.S.4.5 Justification of Specification
3.2.S.6 Container Closure System
3.2.S.7.1 Stability Summary and Conclusions
3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3 Stability Data

3.2.P.1 Description and Composition of the Drug Product
3.2.P.3.1 Manufacturer(s)
3.2.P.3.2 Batch Formula
3.2.P.3.3 Description of Manufacturing Process and Process Controls
3.2.P.3.4 Controls of Critical Steps and Intermediates
3.2.P.4.5 Excipients of Human or Animal Origin
3.2.P.4.6 Novel Excipients
3.2.P.5.1 Specification(s)
3.2.P.5.4 Batch Analyses
3.2.P.5.5 Characterisation of Impurities
3.2.P.5.6 Justification of Specifications
3.2.P.7 Container Closure System
3.2.P.8.1 Stability Summary and Conclusion
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment
3.2.P.8.3 Stability Data

For the following sections, the applicant can submit for each section, one document or multiple documents, e.g. one for each material, step, validation study, study report, reference standard or material, facility, or excipient, as the case may be:

3.2.S.2.3 Control of Materials
3.2.S.2.4 Controls of Critical Steps and Intermediates
3.2.S.2.5 Process Validation and/or Evaluation
3.2.S.2.6 Manufacturing Process Development
3.2.S.4.2 Analytical Procedures
3.2.S.4.3 Validation of Analytical Procedures
3.2.S.5 Reference Standards or Materials

3.2.P.2 Pharmaceutical Development
3.2.P.3.5 Process Validation and/or Evaluation
3.2.P.4.1 Specifications
3.2.P.4.2 Analytical Procedures
3.2.P.4.3 Validation of Analytical Procedures
3.2.P.4.4 Justification of Specifications
3.2.P.5.2 Analytical Procedures
3.2.P.5.3 Validation of Analytical Procedures
3.2.P.6 Reference Standards or Materials

3.2.A.1 Facilities and Equipment
3.2.A.2 Adventitious Agents Safety Evaluation
3.2.A.3 Excipients

For the Pharmaceutical Development section, one document can be provided covering all subsections but an applicant can decide to submit several documents in which case, one document should be provided for each subsection, namely: 3.2.P.2.1, 3.2.P.2.2, 3.2.P.2.3, 3.2.P.2.4, 3.2.P.2.5, and 3.2.P.2.6.

The applicant can submit one document or multiple documents, i.e. one document for each subsection, as defined according to the appropriate regional guidance(s), under 3.2.R Regional Information.

Each copy of a literature reference should be submitted as an individual document under 3.3 Literature References.

2.2 Document Pagination and Segregation

Every document should be numbered starting at page one, except for individual literature references, where the existing journal page numbering is sufficient. It is not considered necessary to display the number as '1 of n' where n is the total number of pages in the document.

(See **2.1. Definition of a Quality Document**.)

Additionally, all pages of a document should include a unique header or footer which briefly identifies its subject matter. In a paper-based drug submission, this same identifier should be used on a tab that precedes the document, to facilitate finding that document within the dossier.

If a section contains more than one document, a specific Table of Contents for that section can be included to identify the chronology and titles of the documents contained therein. e.g.

- Tab with "3.2.S.4.2 Analytical Procedures"
  - Table of Contents, listing the title of Procedure A, Procedure B, Procedure C
- Tab with "3.2.S.4.2 "Procedure A";
  - Procedure A (i.e. document, page 1-n)
- Tab with "3.2.S.4.2 "Procedure B";
  - Procedure B (i.e. document, page 1-n)
- Tab with "3.2.S.4.2 "Procedure C";
  - Procedure C (i.e. document, page 1-n)

If a section contains only a single document (e.g. 3.2.S.1.1 Nomenclature), only a tab identified by "3.2.S.1.1 Nomenclature" should precede the document.

2.3 Table of Contents Formatting

Module 2:

The 2.1 CTD Table of Contents should go down to the third (e.g. 2.3.S) or fourth (e.g. 2.3.S.1) level, depending on how a document is defined for the Quality Overall Summary. (See **2.1 Definition of a Quality Document**.)

Module 3:

The Table of Contents provided under 3.1 should cover the high-level section numbering, the associated section heading, and Volume number, in the order that they appear in the drug submission. This Table of Contents would be used to identify the contents of Module 3 as defined in the M4Q guidance. It should go down to the fifth level only (e.g. 3.2.P.2.1). Note that additional subsections and subheadings are defined in the M4Q guidance beyond this level (e.g. under 3.2.P.2) and this formatting should be used within the dossier, despite not being stated in the 3.1 Table of Contents. The lower level Table of Contents described under **2.3 Document Pagination and Segregation** should be excluded from the 3.1 Table of Contents.

At the applicant's discretion, a Table of Contents can also be included for a particular section that contains multiple documents, in order to identify the chronology and the document subject matter. If there is a desire to introduce additional headers or subsection numbering beyond those which are defined in the M4Q guidance, these should only be included within a document and should not created as a separate document nor as a new

subsection. In this case, a specific Table of Contents for that document can be included to identify the chronology and titles of the subsections contained therein. These documents and subsections should not appear in the 3.1 Table of Contents.

Furthermore, additional attachments or appendices should not be incorporated into this formatting, except as a document under a section where multiple documents might be provided. In this case, a cross-reference should be made within the relevant section to the attached or appended document. If there is a desire to append or attach additional information to a section that is comprised of only one document, this information should be incorporated within that document.

All Table of Contents title entries should either correspond to heading names and section numbering as defined in the M4Q guidance or to identifiers appearing on tabs (for a paper-based drug submission only), preferably by their full title, which should easily identify any abbreviated title which might be used on the corresponding tab. The Table of Contents should not specify any page numbers.

Literature References should be listed in a Table of Contents specific for this section.

2.4 When can separate or repeated sections be appropriate?

There can be a number of instances where repeated sections can be appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a title in parentheses following the CTD 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 it can be appropriate and logical to have information presented separately for a single drug substance. For example, separate sections can be warranted when a single drug substance is made by two significantly different manufacturers or manufacturing processes. However, it is more likely that these different processes will be described within the relevant sub-section of 3.2.S. If the different manufacturing processes also refer to, for example, different specifications, then repeating the whole of the drug substance section is recommended.

Drug Product

Depending on regional requirements, different product presentations (e.g., strengths, container closure configurations, formulations) and/or manufacturing schemes (e.g., aseptic and terminal sterilization) can be submitted in the same dossier. In general, when a single dossier can be submitted, information for each of the product presentations and manufacturing schemes should be combined and presented together in one P section with information provided in the Appendices, and Regional Information sections for each of the product presentations and manufacturing schemes, 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 P section. The majority of the quality information would be identical for the two products. The information that differs between the two would be presented together in the appropriate subsections (e.g., P.7 Container Closure System, P.8 Stability), but would be physically or electronically separated within the subsection.

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

Excipients

If appropriate, where a novel or noncompendial non-novel excipient is proposed, the guidance asks for an Appendix (3.2.A.3) that repeats the format of the drug substance section. It is recommended that the granularity of this Appendix should be the same as the granularity of the drug substance section. In order to assist the construction of the e-CTD, a Data Type Definition (DTD) will be created that replicates the drug substance granularity. There should be a complete section for each novel excipient.

Appendices

There can be occasions where it is appropriate to repeat an Appendix. An example would be 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 harmonised. In this section the documents, their titling and their order should be consistent with the requirements of the region.

2.5 Multiple containers and multiple strengths

There are two containers (PVC blister and PE bottle) for one drug product. The documents for the drug product part in Module 3 are therefore common. Different documents would have to be presented in sections 3.2.P.7 (container closure system) and 3.2.P.8 (stability).

Should full document sets (P1-P8) for both PVC blister and PE bottle be submitted? A similar question would apply for the documents in the case of different package sizes (e.g., 25 tablets, 50 tablets and 1000 tablets in the same container)?

No duplication is necessary. One set of documentation 3.2.P.1 - 3.2.P.8 is needed per one drug product. The information for the blister and the bottle should be presented in the

corresponding sections and where relevant (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.

2.6 Bioanalytical Methods

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

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.

2.7 Drug Master Files

Can the Drug Master File use the CTD format?

Since the DMF systems differ in the three regions, the ICH guidelines do not address this issue. Consequently, the applicant should check with the relevant competent authority in the regions.

3. Multiple links between different sections

Below, examples of multiple references in CTD-Q are proposed. It indicates for some parameters that the information is not necessarily located in one section but needs to be split into different sections.

3.1 Polymorphism

How is information on polymorphism submitted?

- **3.2.S.1.3** If necessary, list the polymorphic form that is present in the proposed active (may be one or more) as characteristics of the drug substance.
- **3.2.S.2.2** Description of manufacturing process and process control Indicates which polymorphic form is synthesised.
- **3.2.S.3.1** Studies performed to identify the potential polymorphic forms of the drug substance. Total number of polymorphs should be listed here and those intended to form the active should be summarised in 3.2.S.1.3.
- **3.2.S.4.1** Specification. If polymorph(s) needs to be defined or limited, it will appear 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 analysis

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

3.3.P.5.1 Specification. If polymorphism needs to be controlled in the drug product, it will appear here.

3.2.P.5.6 Justification of specification (if needed).

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 Particle size

How is information on the particle size for the drug substance submitted?

3.2.S.2.2 Description of manufacturing process and process control
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 analysis
3.2.S.4.5 Justification of specification
3.2.P.2.1.1 and 3.2.P.2.2.1

Identify the influence on particle size on for instance dissolution performance (Q6A decision tree).

3.3 New Location of Quality Information on Investigational Formulations

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

The history of formulation development should be included in Module 3.2.P.2.2.1. A description of batches and the result of batches analyses for the drug product should be included in Module 3.2.P.5.4.

The history of development for the drug substance should be included in Module 3.2.S.2.6. A description of batches and the result of batches analyses should be included in Module 3.2.S.4.4.

This information can also be linked to impurity levels of batches described in 3.2.P.5.5 and 3.2.S.3.2.

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

4. Location Issues in Drug Substance

CTD-Q Section	Issues / Questions	Answers
S 1. General Information		
S 1.1 Nomenclature		
S 1.2 Structure	Should drawings to show secondary and tertiary structures and if applicable, quaternary structures of proteins be provided in 3.2.S.1.2?	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	How much detailed information on the general properties of the drug substance should be included in 3.2.S.1.3?	As per CTD-Q, a list of physicochemical and other relevant properties (e.g., 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 Manufacturer		
S 2.2 Description of the Manufacturing process and Process Controls	Should information on process controls be provided in section 3.2.S.2.2 or 3.2.S.2.4?	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.

CTD-Q Section	Issues / Questions	Answers
S 2.3 Control of Materials	1. Should the discussion and justification of starting materials be included in 3.2.S.2.3?	1. Yes. The discussion and justification of starting materials should be included in 3.2.S.2.3.
	2. Where should analytical procedures for materials described in 3.2.S.2.3 be included?	2. The analytical procedures for the control of materials (e.g., starting materials, reagents, raw materials, solvents) should be presented in section S.2.3. For materials of biological origin, analytical procedures related to adventitious agent safety evaluation should be presented in 3.2.A.2, if applicable.
S 2.4 Control of Critical Steps and Intermediates		
S 2.5 Process Validation and / or evaluation	Where should justification for reprocessing be included?	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 and if validation information is warranted the validation information should be included in 3.2.S.2.5.
S 2.6 Manufacturing Process Development	Should bioavailability / bioequivalence study results that demonstrate product comparability following process changes, be described in 3.2.S.2.6 ?	Reports of Bioavailability / Bioequivalence studies that demonstrate comparability after process changes should be presented in Module 5. Cross references to these reports should be placed into section 3.2.P.2.2.1 in the case of a process change for the drug product manufacture or in 3.2.S.2.6 in the case of a process change for the drug substance manufacturing. A brief summary of the reports can be placed in these sections when considered appropriate.
S 3. Characterisation		
S 3.1 Elucidation of Structure	Where should studies conducted to determine the physicochemical characteristics be included?	Information on the studies conducted to determine the physicochemical characteristics should be included in 3.2.S.3.1. Only a list of the general properties of the drug substance is included in 3.2.S.1.3.

CTD-Q Section	Issues / Questions	Answers
S 3.2 Impurities	1. Should structural characterisation data and a summary of the method of preparation of impurities be included in 3.2.S.3.2?	1. Yes. Such information should be included in 3.2.S.3.2
	2. Where should relevant chromatograms be provided for impurities?	2. ICH Q3A identifies the chromatograms as part of the analytical validation studies. Therefore, relevant chromatograms should be included in 3.2.S.4.3.
	3. Where should nonclinical and clinical data supporting impurity levels be summarised?	3. The qualified level of each impurity with cross-reference to the supporting nonclinical/clinical studies should be included in 3.2.S.3.2.
	4. Should data on impurities reported in batch analyses be included in 3.2.S.3.2 or 3.2.S.4.4?	4. Data on all observed impurities on relevant batches (e.g., clinical, nonclinical, stability) should be provided in 3.2.S.4.4. 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 dossier as appropriate.
S 4. Control of Drug Substance		
S 4.1 Specifications	1. If there are different specification sheets for a drug substance manufacturer, drug product manufacturer and/or applicant, should they all be provided in 3.2.S.4.1?	1. When appropriate, more than one specification sheet should be included in 3.2.S.4.1.

CTD-Q Section	Issues / Questions	Answers
	2. If regulatory and alternative analytical procedures are used to control the drug substance should they both be listed in the specification (3.2.S.4.1)?	2. 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	1. Often times an analytical procedure has changed during the development of the drug substance. If this analytical procedure should be submitted to support the dossier in which section would these analytical procedures be placed?	1. Information on historical analytical procedures used to generate data included in the batch analyses should be included in 3.2.S.4.4
	2. Should an analytical procedure that is only used for stability studies be included in 3.2.S.4.2?	2. No. Information on analytical procedures that are used only for stability studies should be included in 3.2.S.7.3.
S 4.3 Validation of Analytical Procedures		
S 4.4 Batch Analyses	1. Should results from all batches be provided in 3.2.S.4.4?	1. Results from all relevant batches (e.g., clinical, nonclinical, stability), which include those batches used to justify acceptance criteria, should be provided in 3.2.S.4.4.

CTD-Q Section	Issues / Questions	Answers
	2. Should all tests performed be reported even if not included in the specification?	2. Yes, all data from relevant batches should be reported in 3.2.S.4.4.
	3. Where should collated data for a test from multiple batch analyses be presented?	3. If collated data from batch analyses is warranted, the data should be presented in 3.2.S.4.4.
S 4.5 Justification of Specification	1. Should justification for skip testing be included in 3.2.S.4.5?	1. Yes. If skip testing is appropriate, the justification should be included in 3.2.S.4.5
	2. 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 rather than repeating information?	2. Yes. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.

CTD-Q Section	Issues / Questions	Answers
S 5 Reference Standards or Materials	1. Reference standards may be available for the active moiety and impurities. Should information on all reference standards be included in 3.2.S.5? 2. Where should characterisation data for a reference standard be placed in the CTD-Q.	1. If information is required for a reference standard, the information should be included in 3.2.S.5. 2. Characterisation 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 appropriate.
S 6 Container Closure System		
S 7. Stability		
S 7.1 Stability Summary and Conclusions		
S 7.2 Post-approval Stability Protocol and Stability Commitment		
S 7.3 Stability Data	1. Should stress studies be located in 3.2.S.7.3?	1. Yes. Stress studies should be located in 3.2.S.7.3. These data can be referenced for validation of analytical procedures as needed.

CTD-Q Section	Issues / Questions	Answers
	2. Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.S.7.3?	2. Information on historical analytical procedures used to generate the stability data included in 3.2.S.7.3. should be included in 3.2.S.7.3.
	3. Can data from supporting studies be included in 3.2.S.7.3?	3. Yes data from supporting studies can be included in 3.2.S.7.3, if appropriate
	4. Should information on analytical procedures unique to the stability program be presented in 3.2.S.7.3?	4. Information on analytical procedures unique to the stability program should be included in 3.2.S.7.3.
A Appendices	If information for both the drug substance and the drug product should be included in an appendix A.1, how should it be presented?	If drug substance and drug product information is included in the appendices then the preferred presentation is DS first and then DP within each section. For example A.1 (drug substance then drug product) then A.2.
R Regional Information		

5. Location Issues in Drug Product

CTD- Q Section	Issues / Questions	Answers
P 1 Description and Composition of DP	1. Where should information related to the composition of inks used on the drug product be placed?	1. 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 be included in 3.2. P.1 also. In some regions the qualitative composition of proprietary components can be replaced with reference to appropriate DMFs.
	2. Where should information on reconstitution diluents be included?	2. If the diluent is co-packaged with the drug product, the information on the diluent should be placed in a separate P section. If not co-packaged, the compatibility of the diluent with the drug product should be discussed in 3.2.P.2.6.
	3. Should an overfill be indicated in 3.2.P.1?	3. Yes the use of an overfill should indicated in 3.2.P.1. The rationale for an overfill should be included in 3.2. P.2.2.1 (Formulation Development).
	4. Can information on the composition of drug product, other than what is listed in CTD-Q, be included in 3.2.P.1?	4. As needed additional information can be included to adequately describe the composition of the drug product such as (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		

CTD- Q Section	Issues / Questions	Answers
P 2.1 Composition of the DP	1. Where should information on the development of co-packaged diluents be placed ?	1. There should be a separate P section for co-packaged diluents. Choice and development of co-packaged diluents should be included I n3.2. P.2.2.1).
P 2.1.1 Drug Substance	2. Where should a discussion of the drug substance stability or key physicochemical characteristics which might influence the manufacturing process of the drug product be provided?	2. Drug substance stability data should be included in 3.2.S.7 and cross-referenced as needed in3.2. 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).
	3. Where should a discussion of the effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics be provided?	3. Discussion of effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics be provided should be included in3.2.P.2.1.1 .

CTD- Q Section	Issues / Questions	Answers
	4. Where should data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics be provided?	4. 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 [e.g., Q6A Decision Trees 3 and 4 (Part 2)]
P 2.1.2 Excipients	5. 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?	5. Justification for using an excipient if there is evidence of incompatibility should be included in 3.2.P.2.1.1
	6. Where should a discussion of an excipients influence on the manufacturability of the drug product be included?	6. Discussion of excipients that can influence manufacturability of drug product should be included in 3.2.P.2.1.2.
	7. Where should a discussion of the ability of a functional excipient to perform through shelf life be included?	7. Discussion of ability of functional excipients to perform though shelf-life (e.g., antioxidants, penetration enhancers) should be included in 3.2. P.2.1.2.

CTD- Q Section	Issues / Questions	Answers
P 2.2 Description of the Mfg Process and Process Controls	1. Where should tables that describe the composition of formulations used in development studies be included?	1. Tables describing different development formulations should be included in 3.2.P.2.2.1 .
P 2.2.1 Formulation Development	1. Where should information on IVIV correlation be included in CTD-Q?	1. Summarised information on the IVIV correlation should be included in 3.2.P.2.2.1 with inclusion of a cross reference the studies in Module 5.
	2. Can cross-reference be made to bioequivalence information in other Modules?	2. Cross-referencing to both Modules 2 and 5, can be included to facilitate the review process.
	3. Where should information be included to justify a tablet score?	3. The rationale/justification for tablet scoring should be provided in 3.2.P.2.2.1.
	4. Should the release mechanism of the dosage form for controlled release drug products be described in 3.2.P.2.2.1?	4. Description of release mechanism in the dosage form for controlled release drug products should be included in section 3.2.P.2.2.1.

CTD- Q Section	Issues / Questions	Answers
P 2.2.2 Overages	1. Where should overages be justified?	1. Justification for overages should be included in 3.2.P.2.2.2.
P 2.2.3 Physicochemical and Biological Properties	1. Where should any discussion on dissolution development be included?	1. A summary of dissolution development should be included in 3.2.P.2.2.3 with cross reference to studies in Module 5 as appropriate. The justification for the dissolution test should be included in 3.2.P 5.6.
	2. Where should a discussion of the key drug product physicochemical or biological characteristics which might influence the manufacturing process of the drug product be provided?	2. 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.
	3. Where should data from studies on the potential effects of key drug substance physiochemical characteristics on the performance of the drug product be provided?	3. 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 [e.g., Q6A Decision Trees 4 (Part 3) and 7 (Part1)].
P 2.3 Manufacturing Process Development	1. Where should the justification of sterilisation be provided?	1. If required, justification would be included in 3.2.P.2.3

CTD- Q Section	Issues / Questions	Answers
	2. What information on clinical trial formulations should be included in 3.2.P.2.3?	2. Information on clinical formulations would 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	1. Should information on container closure system leachables and extractables be included in 3.2.P.2.4?	1. Yes, information on both are included in 3.2.P.2.4. When warranted, leachables should be included in 3.2.P.5.5 and 3.2.P.5.1 . Also, leachables might be confirmed through shelf-life as part of the formal stability studies and the results would be reported in 3.2.P.8.3.
	2. Where should performance characteristics of a container closure be provided?	2. Information on performance of the container closure system should be included in 3.2. P.2.4 (e.g., priming and repriming studies for metered dose inhalers).
	3. Where should information on studies relating to cleaning of metered dose inhalers be included?	3. Information on cleaning of metered dose inhalers should be included in 3.2.P.2.4.
	4. Where should information on the light protection characteristics of the container closure be provided?	4. 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 is provided in 3.2.P.8.3 (defined as stress study in Q1A/B).

CTD- Q Section	Issues / Questions	Answers
P 2.5 Microbiological Attributes	1. Should discussion of Decision Tree 6 from Q6A be included in 3.2.P.2.5 ?	1. Yes. Discussions relating to Decision Tree 6 (non-sterile drug substance and excipients) and Decision Tree 8 (non-sterile solid) should be provided in 3.2.P.2.5.
P 2.6 Compatibility	1. 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 ? 2. Should compatibility of co-administered drugs be provided in 3.2.P.2.6? 3. Should information on incompatible diluents be provided in 3.2.P.2.6?	1. Information on the compatibility of reconstitution diluents to support claims in the label is included in 3.3.P.2.6. Data from constitution or dilution studies performed as part of the formal stability studies to confirm product quality through shelf life are reported in 3.2.P.8.3. 2. Compatibility with co-administered drugs should be included in 3.2.P.2.6 3. Yes.
P 3 Manufacture		
P 3.1 Manufacturer(s)		

CTD- Q Section	Issues / Questions	Answers
P 3.2 Batch formula	1. Are overages included in 3.2.P 3.2 ?	1. Yes, overages are included in the batch fomula in section 3.2.P.3.2
P 3.3 Description of the Manufacturing Process and Controls	1. Where should reprocessing be described?	1. 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 and if validation information is warranted the validation information should be included in 3.2.P.3.5.
	2. Should critical steps and intermediates be identified in P.3.3?	2. 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.
	3. Should an overfill be identified in 3.2.P.3.3 ?	3. Yes, the overfill should be identified in 3.2.P.3.3.
	4. Should a statement regarding manipulation of ruminant-derived materials in drug product manufacturing facility be included in 3.2.P.3.3. ?	4. A statement regarding manipulation of ruminant-derived materials in drug product manufacturing facility should be included here.. If potential for cross contamination with adventitious agents exist, additional information provided in 3.2.A.1 and or 3.2.A.2.

CTD- Q Section	Issues / Questions	Answers
P 3.4 Control of Critical Steps and Intermediates	1. Is the detailed information on critical steps and intermediates that have been identified in 3.2.P.3.3 included in 3.2.P.3.4?	1. Yes detailed information should be provided in 3.2.P.3.4 for critical steps and all intermediates that are controlled.
	2. 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?	2. Yes. 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
	3. Where should information on the analytical procedures for an in-process material test performed in lieu of a finished product test?	3. 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).
P 3.5 Process Validation and/or Evaluation		

CTD- Q Section	Issues / Questions	Answers
P 4 Control of Excipients	1. Where would additional scientific data for noncompendial, nonnovel excipients be placed?	1. For noncompendial, nonnovel excipients additional scientific data can be included in 3.2.A.3.
P 4.1 Specifications		
P 4.2 Analytical Procedures		
P 4.3 Validation of Analytical Procedures		
P 4.4 Justification of Specifications	1. Where should certificates of analysis or batch data for excipients be included? 2. 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 rather than repeating this information?	1. Certificates of analysis or batch data for excipients should be included in 3.2.P.4.4. 2. Yes. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.

CTD- Q Section	Issues / Questions	Answers
P 4.5 Excipients of Human or Animal Origin	1. Where should information on excipients of human or animal origin be located?	1. Information on excipients of human or animal origin in 3.2.P.4.5. Information on adventitious agent safety evaluation should be included in 3.2.A.2. For 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)	1. Where should release and shelf-life specifications be located?	1. Both specifications are included in 3.2.P.5.1 (see also question for 3.2.P.8.1).
	2. Should an in process test which can take the place of an end-product test be included in the specification. ?	2. Yes. An in-process test that can take the place of an end-product test should be listed in the specification.
	3. If regulatory and alternative analytical procedures are used to control the drug product should they both be listed in the specification (3.2.P.5.1)?	3. Any analytical procedure used to control the drug product, and the associated acceptance criteria, should be listed in the specification.

CTD- Q Section	Issues / Questions	Answers
P 5.2 Analytical Procedures	1. Often times an analytical procedure has changed during the development of the drug product. If this analytical procedure should be submitted to support the dossier, in which section would these analytical procedures be placed?	1. Information on historical analytical procedures used to generate data included in the batch analyses section should be included in 3.2.P.5.4
	2. Should an analytical procedure that is only used for stability studies be included in 3.2.P.5.2?	2. No. Information on analytical procedures that are used only for stability studies should be included in 3.2.P.8.3.
P 5.3 Validation of Analytical Procedures		
P 5.4 Batch analysis	1. 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?	1. 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

CTD- Q Section	Issues / Questions	Answers
	2. Should all tests performed be reported even if not included in the specification?	2. Yes all data from relevant batches should be reported in P.5.4.
	3. Where should collated data for a test from multiple batch analyses be presented?	3. If collated data from batch analyses is warranted, the data should be presented here.
P 5.5 Characterisation of Impurities	1. Should all observed impurities be listed in 3.2.P.5.5 even if they are not included in the drug product specification?	1. Yes, 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)	1. Should justification for skip testing be included in 3.2.P.5.6?	1. Yes. If skip testing is appropriate, the justification should be included in 3.2.P.5.6
	2. 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?	2. Yes. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.

CTD- Q Section	Issues / Questions	Answers
P 6 Reference Standards or Materials	1. Reference standards may be available for the active moiety and impurities. Should information on all reference standards be included in 3.2.P.6? 2. Where should characterisation data for a reference standard be placed in the CTD-Q.	1. If information is required for a reference standard, the information should be included in 3.2.P.6. 2. Characterisation data for the reference standard should be included in 3.2.P.6. Cross reference to information in other sections can be included as appropriate.
P 7 Container Closure System		
P 8 Stability		
P 8.1 Stability Summary and Conclusion	1. Should shelf-life specifications be repeated under this section?	1. Shelf-life specifications should be indicated here and as appropriate in 3.2.P.8.3.
P 8.2 No format comments		

CTD- Q Section	Issues / Questions	Answers
P 8.3 Stability Data	1. Should stress studies be located in 3.2.P.8.3?	1. Yes. Stress studies should be located in 3.2.P.8.3. These data can be referenced for validation of analytical procedures as needed.
	2. Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.P.8.3?	2. Information on historical analytical procedures used to generate the stability data included in 3.2.P.8.3 should also be included in 3.2.P.8.3.
	3. Can data from supporting studies be included in 3.2.P.8.3?	3. Yes, data from supporting studies can be included in 3.2.P.8.3, if appropriate.
	4. Should information on analytical procedures unique to the stability program be presented in 3.2.P.8.3?	4. Yes, information on analytical procedures unique to the stability program should be included in 3.2.P.8.3.
	5. Where should the statistical analysis of the stability data be included?	5. The detailed statistical analysis report, if included, should go in 3.2.P.8.3, but a summary or conclusions of the statistical analysis should go in 3.2.P.8.1.

A Appendices	1. If information for both the drug substance and the drug product should be included in an appendix 3.2.A.1 of a paper submission, how should it be presented?	1. If drug substance and drug product information is included in the appendices then the preferred presentation is DS first and then DP within each section. For example 3.2.A.1 (drug substance then drug product) then 3.2.A.2.