AstraZeneca

0634 '03 FEB 25 10:47

Date: FEB 24 2003

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number [02D-0509]
Response to FDA Call for Comments
International Conference on Harmonisation; Draft Guidance on the M4 Common Technical Document—Quality: Questions and Answers/Location Issues

Dear Sir or Madam:

Reference is made to the December 30, 2002 Federal Register notice announcing the request for comments on, "Common Technical Document—Quality: Questions and Answers/Location Issues" and to the January 9, 2003 Federal Register notice correcting the docket number for document named above.

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Cindy Faulkner, Associate Director Regulatory Project Management at (302) 886-8185.

Sincerely,

Carol Stinson-Fisher

Carol Stinson-Fisher, Associate Director
Technical Regulatory Affairs
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Enclosure

02D-0509

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AstraZeneca's Comments to FDA Docket # 02D-0509

ICH M4Q "Common Technical Document—Quality: Questions and Answers/Location Issues"

General Comments

- AstraZeneca is supportive of the objectives of enabling the implementation of a common format through the CTD, which is also consistent with e-CTD. However, the proposals are in some instances too prescriptive and begin to address the detailed content of the application file.
- In the guidance it should be made clear that this additional guidance is not mandatory and only provides suggestions on how to deal with presentation, format and placement issues. In particular, for placement issues it should be made clear that information need only be supplied, if required. Deviation from the guidance need not be justified, provided information is easily located and is presented under an appropriate module heading.
- Much of the advice concerning publishing is considered to be very helpful, and some additional clarity is requested.
- The final output needs to be ICH focused and not represent a European view. It would be useful for ICH to prepare a dummy published output to provide an example of good practice as outlined in this document.

Specific Comments

Section 1 Introduction

1st paragraph – reword end of paragraph

This document also clarifies location issues where information is required but no explicit guidance is provided in CTD-Q (Modules 2 and 3) in which section it could be presented. (See under 4. Location Issues in Drug Substance and under 5. Location Issues in Drug Product.)

2nd paragraph

The additional guidance does address content. For example under location issues in Drug Substance 3.2.S.4.4, the first two issues discuss detailed content and should be deleted.

Section 2 General Issues

2.1 Definition of a Quality Document

Module 2:

The approach should also include a combination of the approaches. For example 2.3.S could be presented as one document and 2.3.P.1 through to 2.3.P.8 presented as eight documents.

Suggest that this section is rewritten for clarification, to allow greater flexibility and incorporate 2.3 and 2.3.R.

For the following sections of the Quality Overall Summary, the applicant has the option to submit one document with multiple subheadings and subsections, as defined in the M4Q guidance, or one document covering each heading:

2.3	Quality Overall Summary Introduction
2.3.S	Drug Substance
2.3.P	Drug Product
2.3.A	Appendices
2.3.R	Regional Information

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

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
2.3.R.	Regional Information

or a mixture of the above approaches depending on the complexity of the application.

2.3 Table of Contents Formatting

Module 3:
Paragraph #1

It may be helpful to include a more detailed Table of Contents under 3.1 particularly for more complex paper submissions. An appropriate level of section headings should be provided to guide the reviewer to the documentation. The table of contents should be allowed to go down to at least that defined under CTD i.e. the sixth level for Pharmaceutical Development e.g. 3.2.P.2.2.1 Formulation Development.

Paragraph #2

Additional guidance is requested for introduction of subheadings numbering for example for 3.2.P.7 Container Closure System. We would expect subheading numbering 3.2.P.7.1, 3.2.P.7.2 etc... for example to be acceptable guidance and to be included in an overall table of contents and/or appearing on tabs for a paper submission should this facilitate review/location of information.

Section 3 Multiple links between different sections

The title and text is unclear. Suggest that title is changed to Complex Location Issues.

Examples of certain subjects that may need to be addressed in many sections in Module 3 are presented below, together with how the information may be split. Please amend introduction to reflect any changes made.

There could be an additional topic added on Impurities (see Location Issues in Drug Substance 3.2.S.3.2 Impurities).

Sections 4 & 5 Location Issues

Please add a disclaimer that the answers to the issues/questions only provide a suggested location for information when it is a requirement for submission in a particular region. For example in 3.2.P.4.4 Justification of Specifications, certificates of analysis or batch data for an excipient meeting pharmacopoeial (JP, USP, PhEur) requirements may not be required. Indeed all responses could commence with the words "If required."

Comments to specific location issues have been added to the tables below.

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 **of the drug substance, including biological activity for Biotech** should be included in 3.2.S.1.3. **In this document it should be stated clearly which solid state form of the drug substance has been chosen, but discussions and studies conducted on crystal forms and hydrates/solvates could be placed in this document rather than in S.3.1 (Elucidation of structure and other characteristics).**
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? 2. Where should analytical procedures for materials described in 3.2.S.2.3 be included?	1. Yes. The discussion and justification of starting materials should be included in 3.2.S.2.3. 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		

CTD-Q Section	Issues / Questions	Answers
S 3.1 Elucidation of Structure	Where should studies conducted to determine the physicochemical characteristics be included?	**The emphasis on the chemical structure of the drug substance and its verification (Elucidation of structure and other characteristics). Information on the solid state form of the drug substance, e.g. hydrate, solvate, anhydrate or a specific crystal form should also be given here. As noted in CTD guidance** information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs may also be included here. **However, it may be better if other studies conducted to determine the physicochemical characteristics e.g. solid state forms were discussed elsewhere (e.g. in 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? 2. Where should relevant chromatograms be provided for impurities? 3. Where should nonclinical and clinical data supporting impurity levels be summarised? 4. Should data on impurities reported in batch analyses be included in 3.2.S.3.2 or 3.2.S.4.4?	**1. The impurities document should give a comprehensive overview of possible impurities from a theoretical, scientific standpoint and from actual batch data. In addition should show structural formulae, origin of impurities and a discussion/judgment of which impurities have a potential to occur in the drug substance. Description of the syntheses of impurities and/or large amounts of structural elucidation/characterization would make the document difficult to read and not focused. Synthesis/structure elucidation of impurities is background information and should be available on request or provided as regional requirements dictate but not specifically included here. For those impurities that must be available as reference materials (e.g. for system suitability, external standards) information on the synthesis and characterization should be given in S.5 (reference standards and materials).** 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.** The qualified level of each impurity with cross-reference to the supporting nonclinical/clinical studies should be included in 3.2.S.3.2. **The qualified levels of specified impurities (not relevant for others) may also be discussed in S.4.5 (Justification of specification) with appropriate cross-reference to S.3.2 and/or possibly S.4.4 (See also below under Q4) and to the nonclinical and clinical modules. This section could be the subject of "Complex Location Issues."** **4. The US guidance and NtA QOS 2.3.S.3 provides advice that could be followed here.** **3.2.S.3.2 should provide data on potential and actual impurities arising from the synthesis, manufacture, and/or degradation that is the basis for setting the acceptance criteria for individual and total impurities. Information in 3.2.S.3.2 should also include the impurity levels in batches of the drug substance used in the nonclinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. It should be stated in this section how the proposed impurity limits are qualified.** **A tabulated summary of the data provided in 3.2.S.3.2, with graphic representation where appropriate, should be imported directly into 2.3.S.3. This data may also appear in 3.2.S.4.4, alongside the other tests performed on the drug substance.**

CTD-Q Section	Issues / Questions	Answers
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? 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)?	1. When appropriate, more than one specification sheet should be included in 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? 2. Should an analytical procedure that is only used for stability studies be included in 3.2.S.4.2?	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. 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		

CTD-Q Section	Issues / Questions	Answers
S 4.4 Batch Analyses	1. Should results from all batches be provided in 3.2.S.4.4?	1. **Detailed content issue – question should be deleted. It is obvious where appropriate batch analysis data should go in this section.**
	2. Should all tests performed be reported even if not included in the specification?	2. **This is a detailed content issue and question should be deleted.**
	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.
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?	1. If information is required for a reference standard, the information should be included in 3.2.S.5.
	1. Where should characterisation data for a reference standard be placed in the CTD-Q.	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

CTD-Q Section	Issues / Questions	Answers
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? 2. Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.S.7.3? 3. Can data from supporting studies be included in 3.2.S.7.3? 4. Should information on analytical procedures unique to the stability program be presented 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. 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. Yes data from supporting studies can be included in 3.2.S.7.3, if appropriate 4. Information on analytical procedures unique to the stability program should be included in 3.2.S.7.3.
~~**Appendices and Regional Information**~~		**Move these two sections to end of document. Create Location issues in Appendices and Regional Information as Sections 6 & 7?**

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? 2. Where should information on reconstitution diluents be included? 3. Should an overfill be indicated in 3.2.P.1? 4. Can information on the composition of drug product, other than what is listed in CTD-Q, be included in 3.2.P.1?	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. *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. *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. 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
P2.1 Composition of the DP	Where should information on the development of co-packaged diluents be placed?	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).
P2.1.1Drug Substance	1. 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. Where should a discussion of the effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics be provided? 3. Where should data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics be provided?	1. 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 , when discussing key physicochemical characteristics that can influence the performance of the drug product.** 2. Discussion of effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics be provided **may** be included in **3.2.P.2.1.1 or 3.2.P.2.2.1.** 3. Data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics should be provided in **3.2.P.2.2.1** [e.g., Q6A Decision Trees 3 and 4 (Part 2)]

CTD- Q Section	Issues / Questions	Answers
P 2.1.2 Excipients	1. 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? 2. Where should a discussion of an excipients influence on the manufacturability of the drug product be included? 3. Where should a discussion of the ability of a functional excipient to perform through shelf life be included?	1. Justification for using an excipient if there is evidence of incompatibility should be included in **3.2.P.2.1.2 where the choice of excipient is discussed. The compatibility of the excipient used in the drug product is discussed factually in 3.2.P.2.1.1.** 2. Discussion of excipients that can influence manufacturability of drug product should be included in 3.2.P.2.1.2, **under drug product performance.** 3. 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**, under drug product performance**.
P 2.2 Description of the Mfg Process and Process Controls	Where should tables that describe the composition of formulations used in development studies be included?	Tables describing different development formulations should be included in3.2.P.2.2.1 .
P 2.2.1 Formulation Development	1. Where should information on IVIV correlation be included in CTD-Q? 2. Can cross-reference be made to bioequivalence information in other Modules? 3. Where should information be included to justify a tablet score? 4. Should the release mechanism of the dosage form for controlled release drug products be described in 3.2.P.2.2.1?	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. Cross-referencing to both Modules 2 and 5 ,can be included to facilitate the review process. 3. The rationale/justification for tablet scoring should be provided 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	Where should overages be justified?	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? 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? 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?	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. 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. 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? 2. What information on clinical trial formulations should be included in3.2. P.2.3?	1. If required, justification would 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 in3.2. P.2.3.

CTD- Q Section	Issues / Questions	Answers
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 in3.2.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 in3.2. 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 in3.2.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. Photo stability data are provided in 3.2.P.8.3 (defined as stress study in Q1A/B).
P 2.5 Microbiological Attributes	Should discussion of Decision Tree 6 from Q6A be included in 3.2.P.2.5 ?	Yes. Discussions relating to Decision Tree 6 (non-sterile drug substance and excipients) and Decision Tree 8 (non-sterile solid) should be provided in3.2.P.2.5.

CTD- Q Section	Issues / Questions	Answers
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 in3.2.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 in3.3. 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	Are overages included in 3.2.P 3.2 ?	Yes, overages are included in the batch formula in section 3.2.P.3.2
P 3.3 Description of the Manufacturing Process and Controls	1. Where should reprocessing be described? 2. Should critical steps and intermediates be identified in P.3.3? 3. Should an overfill be identified in3.2. 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. ?	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. 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. Yes, the overfill should be identified 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. **Do not understand basis for question. Can this be clarified?**
P 3.4 Control of Critical Steps and Intermediates	1. Is the detailed information on critical steps and intermediates that have been identified in3.2.P.3.3 included in 3.2.P 3.4? 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?. 3. Where should information on the analytical procedures for an in-process material test performed in lieu of a finished product test?	1. Yes detailed information should be provided in 3.2. P.3.4 for critical steps and all intermediates that are controlled. 2. Yes. Critical process control values from relevant batches to support numeric ranges, limits, etc for critical process controls should be included in3.2. P.3.4 3. In3.2. 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).

CTD- Q Section	Issues / Questions	Answers
P 3.5 Process Validation and/or Evaluation		
P 4 Control of Excipients	Where would additional scientific data for noncompendial, nonnovel excipients be placed?	For noncompendial, nonnovel excipients additional scientific data can be included in3.2.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. **If required** Certificates of analysis or batch data for excipients **may** be included in3.2. 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	Where should information on excipients of human or animal origin be located?	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? 2. Should an in process test which can take the place of an end-product test be included 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)?	**1.** Both specifications are included in3.2.P.5.1 (see also question for 3.2.P.8.1). **Release and/or shelf-life specifications will be required here depending on where application made.** 2. Yes. An in-process test that can take the place of an end-product test should be listed in the specification. **Isn't this getting potentially regional specific (EU) guidance?** 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? 2. Should an analytical procedure that is only used for stability studies be included in3.2.P.5.2?	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.** 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 the description of the batches (e.g., batch number, manufacturing site, use) be included in 3,.2.P.5.4? 2. Should all tests performed be reported even if not included in the specification? 3. Where should collated data for a test from multiple batch analyses be presented?	**1. Information describing the batches should be included in 3.2.P.5.4** **2. This is a detailed content issue and question should be deleted.** 3. If collated data from batch analyses is warranted, the data should be presented here.
P 5.5 Characterisation of Impurities	Should all observed impurities be listed in 3.2.P.5.5 even if they are not included in the drug product specification?	Yes, all observed impurities should be listed **above recognized reporting thresholds and if not provided previously in 3.2.1.S3.2 impurities**. Justification for not including an observed impurity in the specification should be included in3.2.P.5.6.

CTD- Q Section	Issues / Questions	Answers
P 5.6 Justification of Specification(s)	1. Should justification for skip testing 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?	1. Yes. If skip testing is appropriate, the justification should be included in 3.2.P.5.6 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.
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 in3.2.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 **that is not included in 3.2.1.S.5**, 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, **if not included in 3.2.1.S.3 or 3.2.1.S.5**. Cross reference to information in other sections **should** be included as appropriate.
P 7 Container Closure System		
P 8 Stability		
P8.1 Stability Summary and Conclusion	Should shelf-life specifications be repeated under this section?	**No, the specifications do not need to be repeated here**.
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 in3.2.P.8.1.

6. Location Issues in Appendix

A Appendices	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?	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 example3.2. A.1 **Facilities and Equipment** (drug substance then drug product).

7. Location Issues in Regional Information

Location issues in Regional Information should be addressed by individual regulatory authorities.