Industry Book of Knowledge

Practical Considerations for eCTD Submissions: Quality Overall Summary (QOS) for Marketing Applications

A compilation of points to consider based on collective experiences from: Abbott, Amgen, Astellas, AstraZeneca, B.Braun Medical, Boehringer Ingelheim, Bristol Myers Squibb, Cephalon, Eli Lilly, Glaxo-Smith Kline, Johnson & Johnson, Merck, Novartis, Pfizer, sanofi aventis, Takeda, Talecris, Wyeth

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Introduction

The Quality Overall Summary (QOS) is a summary document that follows the scope and outline of the Body of Data in Module 3, Quality. The QOS is located in Module 2.3 of the CTD format, and is required for submission of marketing applications. The content requirements for the QOS are defined in the Guidance for Industry M4Q: the CTD-Quality and are not the subject of this document.

There currently is no clear regulatory guidance regarding *eCTD-specific topics* which facilitate the submission and subsequent lifecycle management of the QOS in electronically filed registration applications.

The purpose of this document is to provide a summary of industry experience and practices to date for the preparation of the QOS for the original marketing application and for subsequent product life cycle management activities. Perspectives from both a regulatory strategy and regulatory operations view are discussed. The information provided is based on the business practices and the cumulative experience of pharmaceutical companies working with the health authorities in the EU, US and Canada. The intent is not to standardize implementation practices across industry, but to acknowledge and support many equally valid and diverse approaches to the CMC dossier in an eCTD format. This document will be revised when the regulations change or new information becomes available.

The topics covered in this document are provided as points for consideration when one starts the preparation of QOS using eCTD format for the marketing application and include the following:

- Granularity considerations
- Hyperlink practices between QOS and Module 3 Documents
- Attributes and leaf title considerations for the original registration application and during life cycle management
- Management of multiple drug substance and drug product sections
    - Industry thoughts and practices
    - Build tool capability
- QOS life cycle management for initial submission, during the review period and post approval changes in different regions: US, Europe and Canada
- QOS for drug master file submissions

1. Granularity for Quality Overall Summary

The ICH Guidance "Granularity Document Annex to M4: Organization of the CTD" outlines three levels of allowed granularity for QOS. Companies are using a variety of approaches for the presentation of the QOS. Experience shows that health authorities have accepted each of these approaches without expressing a consistent preference. It is important to consider business processes and regulatory interpretations within an organization when deciding the QOS granularity strategy in an eCTD format dossier. The projected regulatory strategy for a given product and its lifecycle management are primary considerations regarding the granularity of the QOS.

1.1 Industry Thoughts and Experiences

1.1.1 The single QOS file

ICH allows the submission of a *single document* under Module 2.3 Quality Overall Summary which includes the sections 2.3 Introduction, 2.3.S, 2.3.P, 2.3.S and 2.3.R. This particular approach can be efficient if few changes are anticipated in the document or if there is no intention to update the QOS document in later amendments and post approval changes. However, once the QOS is submitted in this form, replacing the single file with multiple files for mid-range or maximum granularity will be challenging.

1.1.2 The mid-range granularity QOS

According to ICH, the mid-range granularity consists of separate documents under each of the following heading sections:

- 2.3 Introduction
- 2.3.Drug Substance
- 2.3.Drug Product
- 2.3.Appendices
- 2.3.Regional

This approach is a compromise between the single file and maximum granularity options. It would include the highest level headings of the QOS, allowing for fewer files to maintain under lifecycle management principles.

1.1.3 The Maximum Granularity QOS

This approach includes the maximum granularity of the QOS (as outlined below). If the company's business practice and strategy includes a practice to keep a living QOS after the approval, this can be an attractive option. This maximum granularity approach can be beneficial if new data and multiple changes are anticipated after approval of the product. Authors need only to update the sections that have changed, reducing the amount of reviewed information that would be resubmitted.

- 2.3 Introduction
- 2.3.S Drug Substance
  - 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 Standard or Materials
  - 2.3.S.6 Container Closure
  - 2.3.S.7 Stability
- 2.3.P Drug Product
  - 2.3.P.1 Description
  - 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 Standard or Material
  - 2.3.P.7 Container Closure
  - 2.3.P.8 Stability
- 2.3.A Appendices
- 2.3.R Regional Information

2. Hyperlink Practices between QOS and Module 3 Documents

Hyperlinks serve as an aid to the reviewer and should be judiciously determined. Consideration should be made towards the effect of lifecycle actions on the dossier when establishing hyperlink standard practices. Leafs that are later replaced or deleted may have outdated hyperlinks.

2.1 Industry Thoughts and Experiences

In the case of cross references to a specific Module 3 section or specific document within a section, a hyperlink may not be necessary. The majority of viewing tools provide an outline/explorer view of the overall submission where these section headings are easily visible and a single click will take the reviewer to the referenced Module 3 section.

In contrast, cross references to specific items within section documents (e.g. tables, figures, etc.) or destinations outside of Module 3 could be hyperlinked.

Note that some review tools do not include a feature to return to the previous location. In this case, once a reviewer follows a hyperlink to a leaf document outside of the QOS, they may not be able to return easily to the QOS without the aid of the outline/explorer and could lose their place in the QOS document as a result.

Some companies do not include any hyperlinks in the QOS, relying solely on references to Module 3 section numbers. For this approach, it may be helpful to repeat key information (e.g. the specification table) or be specific in discussion as needed to ensure a clear and comprehensive summary of the Module 3 body of data.

3. QOS Attributes and Leaf Title Considerations

3.1 Attributes

The designation of attributes for the Module 2.3 QOS is directly influenced by the eCTD build tool in use within each individual company. For example,

- Some build tools will allow attributes for the Module 2.3 QOS and Module 3 to be entered separately, thereby providing the flexibility to designate different attributes between the two Modules.
- Alternatively, some build tools will automatically duplicate the designated Module 3 attributes for the Module 2.3 QOS.

The eCTD build tool also influences the view of the Module 2.3 QOS.

- With many build tools, if the Module 2.3 QOS or any of the sub-sections of Module 2.3 (e.g., 2.3.1, 2.3.2, etc.) do not contain a document, then the compiled eCTD output will not show those sections.
- Alternately, some build tools have a prescribed granularity for Module 2.3, and display the number of pre-set headings regardless of the number of documents provided in the QOS.

3.2 Leaf Titles

Whether the Module 2.3 QOS is provided as a single document or a series of multiple documents, the leaf title(s) should be descriptive and allow the reviewer to be able to identify the document. This consideration should also be applied to QOS document(s) being submitted during review and/or life cycle to facilitate the differentiation between multiple documents and the corresponding changes.

Approaches to naming conventions for leaf titles may be referenced in the Industry Book of Knowledge “Practical Considerations for eCTD Submissions: A CMC Perspective”. The leaf title should be descriptive and clear to both the reviewing agency and company and does not need to repeat the CTD section name or number. It may be useful to place distinguishing information at the beginning of the leaf title in order to differentiate between documents at the same CTD level.

4. Management of Multiple Drug Substances and Drug Products

When multiple drug substance and drug product sections are provided in Module 3 (i.e., products with multiple 3.2.S and 3.2.P sections), granularity of Module 2.3 QOS depends on the company's desired business practices and the limitations of the software tools.

4.1 Industry Thoughts and Experiences

Below are some examples of strategies that could be considered for Module 2.3 QOS for combination products and products with multiple 3.2.S and 3.2.P sections.

4.1.1 Single QOS Document

Table 1 outlines the approach using a single document for Module 2.3 QOS regardless of the number of DS and DP sections in Module 3. If desired or requested by an agency, the sponsor will update the entire document regardless of the amount of new information that is included. For ease of review a clear outline or roadmap of the information presented should be provided.

Table 1–Single Module 2.3 QOS

CTD Module	Item	Comments
Module 2	2.3.QOS* -or- 2.3 Introduction	Single pdf document, used when minimal life cycle management is anticipated.
Module 3	Full Module 3 Granularity.	One or more documents for each CTD heading, as appropriate.

*Some build tools may not allow one single pdf directly under the heading 2.3 QOS, 2.3 Introduction may be the first location that allows insertion of a document.

4.1.2 Multiple Drug Substance Sections with Common Information

In the case where a marketing application contains multiple 3.2.S sections with shared information, e.g., DS used for parenteral and non-parenteral DP or DS made in multiple manufacturing sites, a separate pdf can be provided under the relevant 2.3.S granular sections. This approach as outlined in Table 2 will work if there are common sections within the 2.3.S.

Table 2 – Multiple Drug Substance Sections with Common Information

CTD Module	Item	Comments
Module 2	2.3 Introduction 2.3.S Drug Substance-Drug A-**Common** 2.3.S.1 General Information 2.3.S.3 Characterization 2.3.S.5 Reference Standard or Materials 2.3.S.6 Container Closure 2.3.S Drug Substance-Drug A-**Site A** 2.3.S.2 Manufacture 2.3.S.4 Control of Drug Substance 2.3.S.7 Stability 2.3.S Drug Substance-Drug A-**Site B** 2.3.S.2 Manufacture 2.3.S.4 Control of Drug Substance 2.3.S.7 Stability 2.3.P Drug Product 2.3P.1 to 2.3P.8.	Appropriate for keeping a live QOS and maximum granularity Depending on the capability of the build tool, the approach outlined here can be accomplished: several 2.3.S folders can be generated from the tool, the output will only shows the relevant sections that have the documents placed under the sections. By contrast, some tools will display all sections within a 2.3.S, whether or not a document exists.
Module 3	Full Module 3 Granularity. 3.2.S Drug Substance-Drug A-**Common** 3.2.S.1 to 3.2.S.7 3.2.S Drug Substance-Drug A-**Site A** 3.2.S.1 to 3.2.S.7 3.2.S Drug Substance-Drug A-**Site B** 3.2.S.1 to 3.2.S.7	One or more documents for each CTD heading, as appropriate.

4.1.3. Multiple Drug Substance Sections in Combination Product

Table 3 is an example of a combination product where there are different 3.2.S drug substance sections and one 3.2.P drug product section.

Table 3 – Multiple Drug Substance Sections in Combination Product

CTD Module	Item	Comments
Module 2	2.3 Introduction 2.3.S Drug Substance-**Drug A**-manufacturer 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 Standard or Materials 2.3.S.6 Container Closure 2.3.S.7 Stability 2.3.S Drug Substance-**Drug B**-manufacturer 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 Standard or Materials 2.3.S.6 Container Closure 2.3.S.7 Stability 2.3.P Drug Product 2.3P.1 to 2.3P.8	Appropriate for keeping a live QOS and maximum granularity The midrange granularity approach is also appropriate by placing single files under each 2.3.S., and 2.3.P sections. Minimal life cycle management may be appropriate using this approach.
Module 3	Full Module 3 Granularity.	One or more documents for each CTD heading, as appropriate.

4.1.4 Multiple Drug Product Sections in Combination Product

Two examples are provided in the case of one 3.2.S section and multiple 3.2.P sections (i.e., different processes and formulations). The first example (Table 4) provides maximum granularity for ease of review and life cycle management. The second example (Table 5) provides a single pdf document for all drug product presentations and the entire document is updated regardless of what new information is included.

Table 4 – Multiple Drug Product Sections in Combination Product (Example 1)

CTD Module	Item	Comments
Module 2	2.3 Introduction 2.3.S Drug Substance-**Drug A**-manufacture 2.3.S.1 to 2.3.S.7 here 2.3.P Drug Product-**Dosage form A**-manufacture 2.3.P.1 Description 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 Standard or Material 2.3.P.7 Container Closure 2.3.P.8 Stability 2.3.P Drug Product-**Dosage form B**-manufacture 2.3.P.1 Description 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 Standard or Material 2.3.P.7 Container Closure 2.3.P.8 Stability	Appropriate for keeping a live QOS and maximum granularity The midrange granularity approach is also appropriate by placing single files under each 2.3.S., and 2.3.P sections. Minimal life cycle management may be appropriate using this approach.
Module 3	Full Module 3 Granularity.	One or more documents for each CTD heading, as appropriate.

Table 5 – Multiple Drug Product Sections in Combination Product (Example 2)

CTD Module	Item	Comments
Module 2	2.3 Introduction 2.3.S Drug Substance-**Drug A**-manufacture 2.3.S.1 to 2.3.S.7 2.3.P Drug Product-**Dosage forms A and B**-manufacture 2.3.P.1 to 2.3P.8	One pdf for all drug product presentations in one 2.3.P section. This might be a workable option for company that does not update the QOS.
Module 3	Full Module 3 Granularity.	One or more documents for each CTD heading, as appropriate.

4.1.5 Build Tool Capability

Currently, there is no single industry standardized eCTD build tool or viewing tool used by companies. Some tools allow the attributes for Module 2 and Module 3 to be entered separately thus allowing different attributes between Module 2 and 3. Some tools will create Module 2 with the same attributes as that of Module 3

Empty folders and unused granularity subsections should not appear in the eCTD output, which provides some flexibility in how the submissions can be structured. For an example, if Module 2.3 or any of the subsections for Module 2.3 (2.3.1, 2.3.2, etc) do not contain a document, the compiled eCTD output will not show those sections- they are simply missing and have no impact the structure of Module 3.

The placement of leaf elements (documents) in the backbone can be different depending on the viewing tool used. For example, a sponsor may place a single file under the heading of 2.3 QOS, but if a viewing tool is used which is from a different vendor than used for the eCTD build, the display may show the document under 2.3 Introduction.

5. Lifecycle Management for Quality Overall Summary

In this section, industry experience with regulatory authorities (FDA, EMA and Health Canada) on the life cycle management of the QOS during the review of the applications and post approval changes are discussed. Designation of the Operators (New, Replace, Delete or Append) will be required for the QOS document that is updated during life cycle. The principles discussed in the Industry Book of Knowledge “Practical Considerations for eCTD Submissions: A CMC Perspective” also apply to QOS life cycle management. Typically, during the review of an application or when companies choose to keep a living QOS after the approval, a “Replace” operator is applied when QOS is updated. When a QOS is submitted specifically reflecting only the post approval changes (or variations), a “New” operator is typically used.

5.1 For US FDA Submission

There is currently no guidance or mandate from FDA regarding maintenance of the QOS either during initial NDA review or for supplements. Some companies choose to update the QOS once the application is approved. Others do not update the QOS unless specifically requested to do so by the Agency. The choice depends on the company's internal processes. Those that update the QOS have submission-ready documents for other regions. Those that do not update the QOS consider it a snap-shot in time, relevant to the sequence under review, with the current, controlled documents for manufacturing and control of the product being located in Module 3.

A variety of approaches are taken with respect to post-approval changes. Some companies do not submit a QOS with supplements. Other companies choose to keep a living QOS with the concern that if the QOS is not updated, a non-Chemistry reviewer (e.g., a Biopharmaceutics reviewer) may review outdated information, leading to incorrect conclusions. Some companies base their decision to include the QOS on the scope of the changes. QOS granularity is an important factor in the decision whether to include the QOS with supplements. Maintaining a living QOS (e.g., updating the existing QOS documents) is facilitated by use of the maximum allowed granularity. Companies who choose to file a QOS with supplements may also use 2.3 Introduction to summarize the changes. Alternatively, a new QOS can be submitted with each supplement; however Module 2.3 can become cluttered after submission of multiple supplements and naming conventions used for the leaf titles will be important. While ICH limits the QOS to one document at each level, some eCTD builder software allows multiple documents.

5.2 For EMA Submission

The Quality Overall Summary for the EU is provided as part of the original marketing application. The QOS replaced the Part II Expert Report as the company's assessment of the CMC information. It is used by many European Agencies as a reviewing aide; therefore, Word documents are required with the submission to allow for electronic copy and paste to the Agency's Assessment report. Update of the QOS during review or upon approval is not mandated by legislation, but may be requested by an agency. Some companies choose to maintain an up-to-date QOS to facilitate filings in other markets and subsequent Type II variations in EU.

Type II variations in EU require submission of a QOS. The QOS need only address those sections updated by the variation. The company must determine whether the QOS document will be filed with an operation attribute of "new", "replace" or "append" to the original document. Companies that maintain an up-to-date QOS with a maximum granularity approach may file the impacted documents using "replace". Other companies choose to file a submission-specific QOS using "new" or "append". The content of the changes and prior selection of granularity for the QOS will have an impact on this decision. The "Append" operator should be used cautiously; a proposal of removing the "Append" operator has been discussed in a recent industry and regulatory conference.

5.3 For Health Canada Submission

Health Canada deems the QOS important and typically requests that it is updated as changes are made resulting from clarifaxes issued during the review of the NDS or post approval submissions. Health Canada may request that the QOS be maintained during review; however,

they sometimes allow companies to update the QOS as the approval time approaches and all queries have been addressed rather than requiring that it be updated with each applicable clarifax response. Some within industry have experiences where Health Canada did not require the QOS to be updated but instead focused on the CPID as the document to be maintained.

Health Canada requires a QOS to be provided with each Level 1 and Level 2 change submitted to Health Canada. It is permissible that the QOS accompanying a Level 1 or Level 2 submission may only include information related to the sections impacted by the Level 1 or Level 2 change. Some companies however, have chosen to maintain the QOS as a living document and will update the relevant section(s) that are impacted by a given Level 1 or Level 2 change.

The QOS is provided to Health Canada in two formats (paper and electronic as WORD file) – the electronic version allows Health Canada to copy text for insertion into their review documentation.

Recent experience with the Health Canada for applications containing multiple drug substances or multiple drug products suggested that the Health Canada has requested the approach of mid-range granularity where QOS-CE consisting of one single file under each of the sections: 2.3 Introduction, 2.3.S, 2.3.P, 2.3.A and 2.3.R.

6. QOS for US Drug Master Files

The drug master files (DMFs) may be submitted following the format recommended in the "Guidance for Industry M4Q: The CTD - Quality". However, there is no regulatory requirement to submit the DMF in CTD or eCTD format. The FDA DMF website has indicated that for Type II DMFs filed in CTD-Q format, a Module 2 is expected. However, the current practice in industry indicates that a QOS is not usually submitted due to the fluid and open nature of the DMF review process.