TABLE 12: The Quality Overall Summary: Making the Best of It

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SCOPE:

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS is a mandatory for most countries and is located in Module 2.3 of the CTD. Detailed guidance on the content is provided in ICH M4Q. It is not clear in the health authority guidance documents how these summaries are used during the review of the initial marketing application as well as throughout the product’s lifecycle. This table will discuss the potential value the QOS could offer to improve the review process and post approval maintenance of the application. Table members will discuss experiences and align on key content that could enhance the QOS.

QUESTIONS FOR DISCUSSION:

1. How might the QOS be used to aid a review of an initial marketing application or post approval submission? Who are the primary users of the QOS: Quality reviewers, cross functional (clinical, PK, toxicology, etc) reviewers, Health Authority management, other?

2. Discuss table members’ experience:
   a. Is the QOS updated [replace in eCTD] during the initial review?
   b. Is it updated [replace in eCTD] during a submission for a post approval change or is updated content provided as a new QOS section [new in eCTD]?
   c. Are hyperlinks to Module 3 used in the QOS? If so, are they maintained or allowed to break during lifecycle?
   d. Do sponsors follow the 80 page length guidance in ICH? What is the appropriate level of detail to include in the QOS?

3. The FDA Draft Guidance on Established Conditions suggests that a summary of the established conditions be included in the Introduction to the Quality Overall Summary because it will ease the review and facilitate identification and discussion of established conditions. The table can discuss why this use of the QOS is recommended and how it would be managed including potential implications to lifecycle.

NOTES:

4. How might the QOS be used to aid a review of an initial marketing application or post approval submission? Who are the primary users of the QOS: Quality reviewers, cross functional reviewers (clinical, PK, toxicology, etc), other?
This group had sponsors and regulators from Health Canada and the US

- Industry sponsor participants:
  - In the US, sponsors often do the QOS under tight timing after the Module 3 is complete
  - Many sponsors cut and paste information from Module 3 – which is a change from the initial expert reports required in the EU
    - There was discussion around how useful cutting and pasting was.
    - Many sponsors are trying to find ways to make the QOS more useful – ie, evaluating whether established conditions should go here;
    - Currently some sponsors are using QOS for holistic summary of where all control strategy pieces can be found in Module 3

- Health Agency Participants:
  - Generally, agency participants would like the QOS to be a true summary that they can read to get a good overall perspective of the submission without all the detail in Module 3
  - QOS can be helpful to tell the story, especially for a complex QbD document
  - One purpose of the QOS for agencies is for use in filling out the assessment reports
    - Health Canada also uses the QOS as the basis for their review report
    - Several sponsors noted they provide the QOS in word format to EU for the assessment report

- Would another reviewer outside of CMC typically look at CMC QOS?
  - Likely only for specific issue

5. Discuss table members’ experience:
   a. Is the QOS updated [replace in CTD] during the initial review?
      i. Sponsors rarely update the QOS during response period for initial FDA questions for FDA due to lack of time
      ii. Canada may ask for updated QOS during review; the CPID is really most important
   b. Is it updated [replace in CTD] during a submission for a post approval change or is updated content provided as a ‘new’ QOS section?
      i. No standard from sponsors
      ii. Some sponsors provide only the QOS section which had changes
      iii. For complex changes, agencies may find the entire QOS helpful, but with statements to identify if nothing from the prior QOS changed
      iv. Health Canada participant noted that there are two separate guidances from Canada, one requiring a QOS be submitted for changes, one not requiring:
         1. Sponsor recommendation to Health Canada for updating guidance was to allow sponsor to determine if submitting the entire QOS was necessary
   c. Are hyperlinks to Module 3 used in the QOS?
      i. Sponsors, only the initial sequence is linked – so only useful as initial review aid
      ii. Health Canada participant finds hyperlinks in the QOS useful
d. Do sponsors follow the 80 page length guidance in ICH? What is the appropriate level of detail to include in the QOS?
   i. Agency participants’ perspective is that sponsors provide extremely long biologic QOS @ 300 pages
      1. It would be more beneficial for Agencies if QOS were shorter
   ii. Recommendation from Health Canada participant for levels of detail:
      1. Include summary tables for P.8.1 and P.8.2. P.8.3 stability date should not be included
      2. Method validation could include only a table per method listing parameters tested, acceptance criteria, and results
      3. Most raw data should be left in Module 3
      4. Helpful to have critical quality attribute criteria and listing in QOS

e. When do sponsors provide updated QOS to agencies?
   i. Sponsors typically provide QOS updates for EU and Canada; specifically Type 2 changes for EU
   ii. One sponsor had a recent example where UK wanted QOS updated for the first time in 6 years for a post-approval supplement
   iii. Not all sponsors update the QOS for US post-approval changes

6. The FDA Draft Guidance on Established Conditions suggests that a summary of the established conditions be included in the Introduction to the Quality Overall Summary because it will ease the review and facilitate identification and discussion of established conditions. The table can discuss how this would be managed and potential implications to lifecycle.
   a. Some sponsors were surprised by FDA guidance to suggest established conditions be located in the QOS since QOS isn’t “required” to be updated for post-approval changes in US
   b. Generally the Agency participants find the QOS helpful
   c. Sponsors are not always convinced of the value of the QOS, and some would like to do away with the QOS
   d. Have any sponsors provided established conditions in intro to QOS?
      i. Some sponsors have submitted established conditions to intro to QOS but filings have yet been approved

7. Who writes the QOS in sponsors companies?
   a. For the majority of sponsors, it is regulatory affairs

8. What other places in submissions do reviewers from Agencies check for changes?
   i. Canada: advises sponsors to use Module 1 Notes to a reviewer for telling story about what is replaced and why; US uses as well
   ii. FDA and Canada read cover letters
   iii. Sponsors are concerned about lot of redundancies with documentation which could cover changes to previous filings – cover letters, application forms, Module 1, QOS

9. For ICH Q12, where are agencies expecting established conditions?
   a. US – guidance suggests Intro to QOS
   b. Plan in Canada to have appendix to CPID to house established conditions