eCTD: A Reviewer's Perspective

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Outline

- Overview
- Observations
  - Pagination
  - Links, bookmarks
  - Topic discontinuity
  - Hierarchical organization
  - Leaf titles
  - Excipients
  - Statistical analysis
- General Comments and Best Practices

Overview

Not all reviewers have experience with eCTD

- Email poll of ~200 reviewers
- "Have you reviewed an eCTD application?"
  - Yes: 78
  - No: 22
  - Not Sure: 5

Global Submit (GS) 4.0: review tool /viewer

- Installed on all CDER PCs
- Also available in field offices

Pagination

Concerns

- Difficult to refer to specific NDA item (compared to paper, e.g. Vol 1, pp 255 to 258)
- Simple modifier (e.g. “refer to page 17) could refer to multiple sections of the CMC data package.
- Total pages in section not always clear to reviewer
- Pages in PDF do not always correspond to page numbers in document.

Pagination (continued)

Current reviewer practice

- Add as much description as possible when referring to a part of an eCTD NDA.
- Scan and insert applicable tables directly
- Avoid using page numbers

What Applicants can do

- Include header or footer that identifies the file for review reference
- Include total pages in footer (i.e., page 17 of 59)

Bookmarks & Links

Concerns

- PDF files with missing or minimal Bookmarks
- Files with few links or links at the doc level
- Non-operational links
- No links for moving backwards in submission

Bookmarks & Links (continued)

Current reviewer practice

- Navigate carefully. Record links or documents needed for further review and search.
- Navigate empirically

What Applicants can do

- Provide PDFs with Bookmarks
- Provide files with specific links from logical places to relevant, specific items
- At end of document, provide links to beginning of next document
- Specify (and provide links for) locations of additional related information

Quality Topic Discontinuity

Concerns

- One topic is often difficult to track
- Many topics are split between multiple locations

(e.g. drug polymorphism-related information appears in 15 sections!)

Quality Topic Discontinuity (continued)

Current reviewer practice

- Completely assess quality topic when introduced
- Revisit pertinent review section and add information accordingly

What Applicants can do

- Specify (and provide links for) locations of additional related information.
- List pertinent (or major applicable) sections in QOS

Hierarchy Too Deep

Concerns

- Navigation to lowest level requires many clicks
- Getting lost
- Difficulty getting back to start

Hierarchy Too Deep

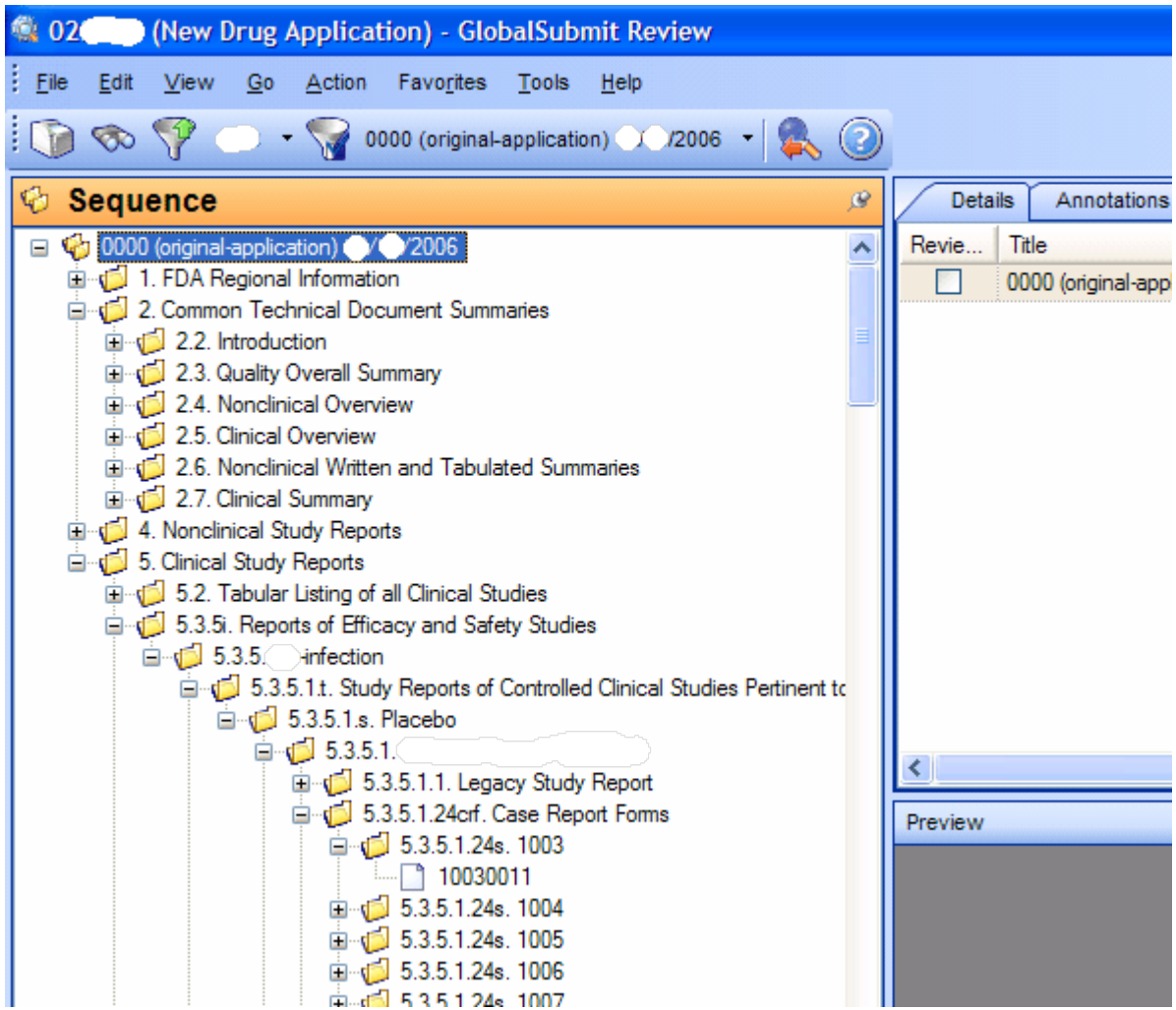
Current reviewer practice

- Navigate to lowest level and review; start over in navigation in order to revisit a higher level (time-consuming)

What Applicants can do

- Provide link to overall beginning of next document at end of PDF (a way of navigating)

Hierarchy Too Deep



Leaf Titles

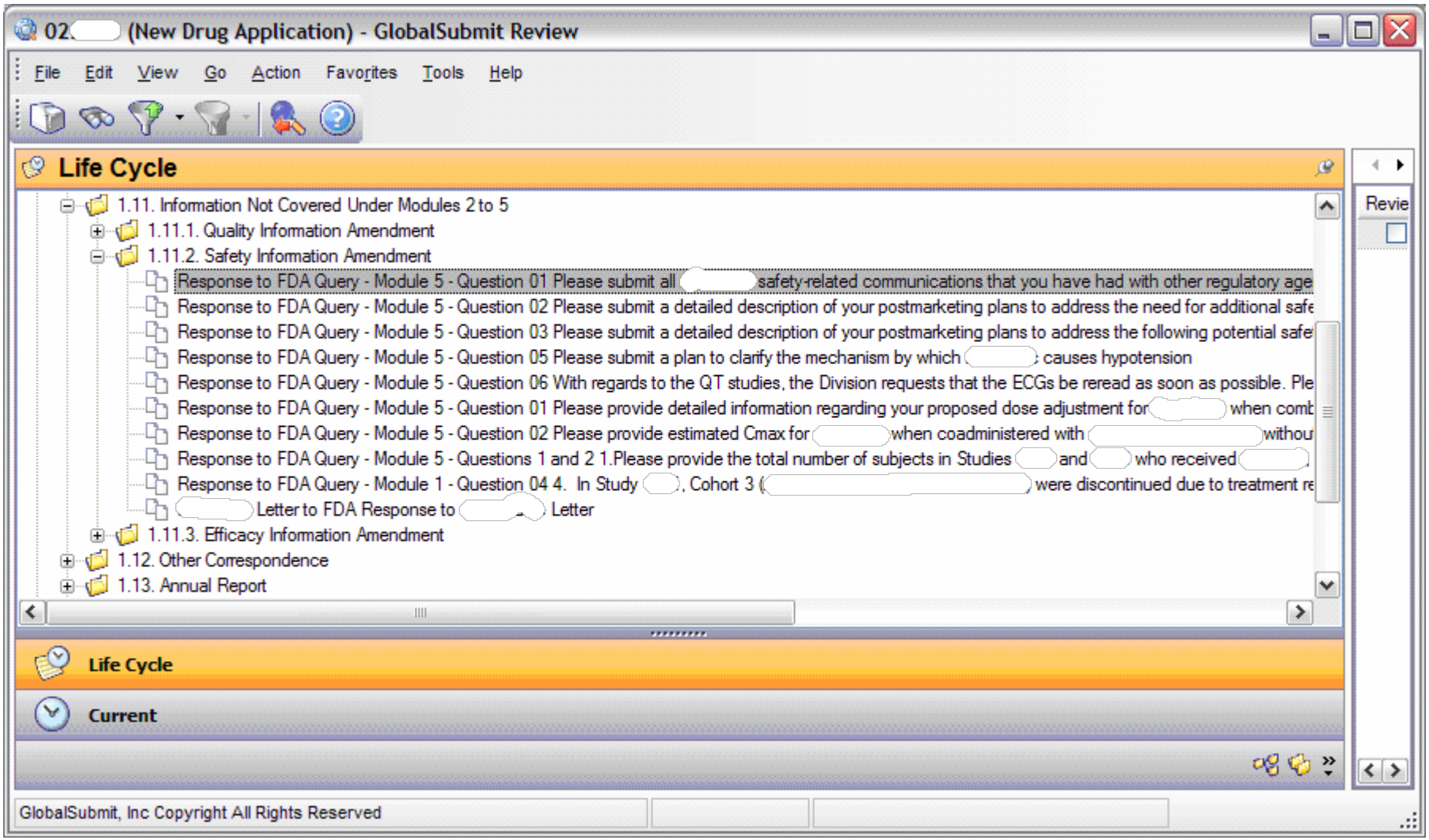
Concerns

- Too long
- Not descriptive

What applicants can do

- Use shorter, meaningful names

Leaf Titles


02 (New Drug Application) - GlobalSubmit Review
File Edit View Go Action Favorites Tools Help
Life Cycle
1.11. Information Not Covered Under Modules 2 to 5
1.11.1. Quality Information Amendment
1.11.2. Safety Information Amendment
Response to FDA Query - Module 5 - Question 01 Please submit all safety-related communications that you have had with other regulatory age
Response to FDA Query - Module 5 - Question 02 Please submit a detailed description of your postmarketing plans to address the need for additional safe
Response to FDA Query - Module 5 - Question 03 Please submit a detailed description of your postmarketing plans to address the following potential safe
Response to FDA Query - Module 5 - Question 05 Please submit a plan to clarify the mechanism by which causes hypotension
Response to FDA Query - Module 5 - Question 06 With regards to the QT studies, the Division requests that the ECGs be reread as soon as possible. Ple
Response to FDA Query - Module 5 - Question 01 Please provide detailed information regarding your proposed dose adjustment for when comb
Response to FDA Query - Module 5 - Question 02 Please provide estimated Cmax for when coadministered with withou
Response to FDA Query - Module 5 - Questions 1 and 2 1.Please provide the total number of subjects in Studies and who received
Response to FDA Query - Module 1 - Question 04 4. In Study , Cohort 3 (were discontinued due to treatment re
Letter to FDA Response to Letter
1.11.3. Efficacy Information Amendment
1.12. Other Correspondence
1.13. Annual Report
Revie
Life Cycle
Current
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Repeated Excipients Section

- Spec* suggests repeated sections with “Attributes” for excipient names

  eCTD Specification (v 3.2, p 4-19)

- Could lead to many small files with little content, particularly for compendial excipients
- However, spec “Comment” suggests that all compendial excipients could be in one file

*See ICH Spec Link: estri.ich.org/eCTD/eCTD_Specification_v3_2.pdf

Excipients Example

- **P.4 Control of Excipients** excipient="compendial"
  - P.4.1 Specifications
  - P.4.2 Analytical Procedures
  - P.4.3 Validation of Analytical Procedures
  - P.4.4 Justification of Specifications
- **P.4 Control of Excipients** excipient="salcaprozate"
  - P.4.1 Specifications
  - P.4.2 Analytical Procedures
  - P.4.3 Validation of Analytical Procedures
  - P.4.4 Justification of Specifications
- **P.4 Control of Excipients** excipient="AYKM"
  - P.4.1 Specifications
  - P.4.2 Analytical Procedures
  - …

(See www.fda.gov/cder/guidance/7042fnl.htm)

Statistical Analysis (Stability)

Concerns

- Not always clearly specified with separate link
- Often attached to copious stability data and difficult to locate
- Stability data used for analysis not clearly stated

Statistical Analysis (Stability)

Current reviewer practice

- Generate information requests when needed
- Generate consults when/if analysis is located

What Applicants can do

- Clearly specify that statistical analysis has (or has not) been performed, along with rationale
- Include description in summary section, with link to S7.3 or P8.3

Stability Data Standard Pilot

- HL7 XML-based stability data file pilot
- Announced in **Federal Register** Vol. 71, No. 94 / Tuesday, May 16, 2006, 28353
- Participants from human and animal pharmaceutical firms
- Four sample data sets submitted
- Viewer developed by **up to data** (http://www.uptodata.de/)
- Demos at CVM, CBER, planned for CDER

General Comments

General Comments – Reviewer Practices

- Submission review is not always linear in strategy
- Several rotating submissions at any given time
- Often submissions are partially reviewed and then tabled depending on workload
- Reviews often conducted via a “topic-by-topic” approach
- Amendments not always reviewed at same time as original submission
- GS Review training would be useful (manual)

Best Practices

Best Practices

- Include meaningful links & Bookmarks
- Confirm that links work
- Include header or footer that identifies the file
- Limit submission of many small files
- Include short descriptive leaf titles
- Be consistent
- Perform QA as a reviewer (e.g., view topics as “stories”)

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