e-SUBMISSIONS: A Clinical Reviewer's Perspective

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Disclaimer

- Views expressed in this presentation are those of the speaker and not, necessarily, of the Food and Drug Administration.

Overview

- **Background:** Life of a clinical reviewer
- **Aspects of Quality e-submissions**

Life of a clinical reviewer

- Most are physicians with variable IT knowledge
- Responsible for reviewing all clinical data

Life of a clinical reviewer

IND

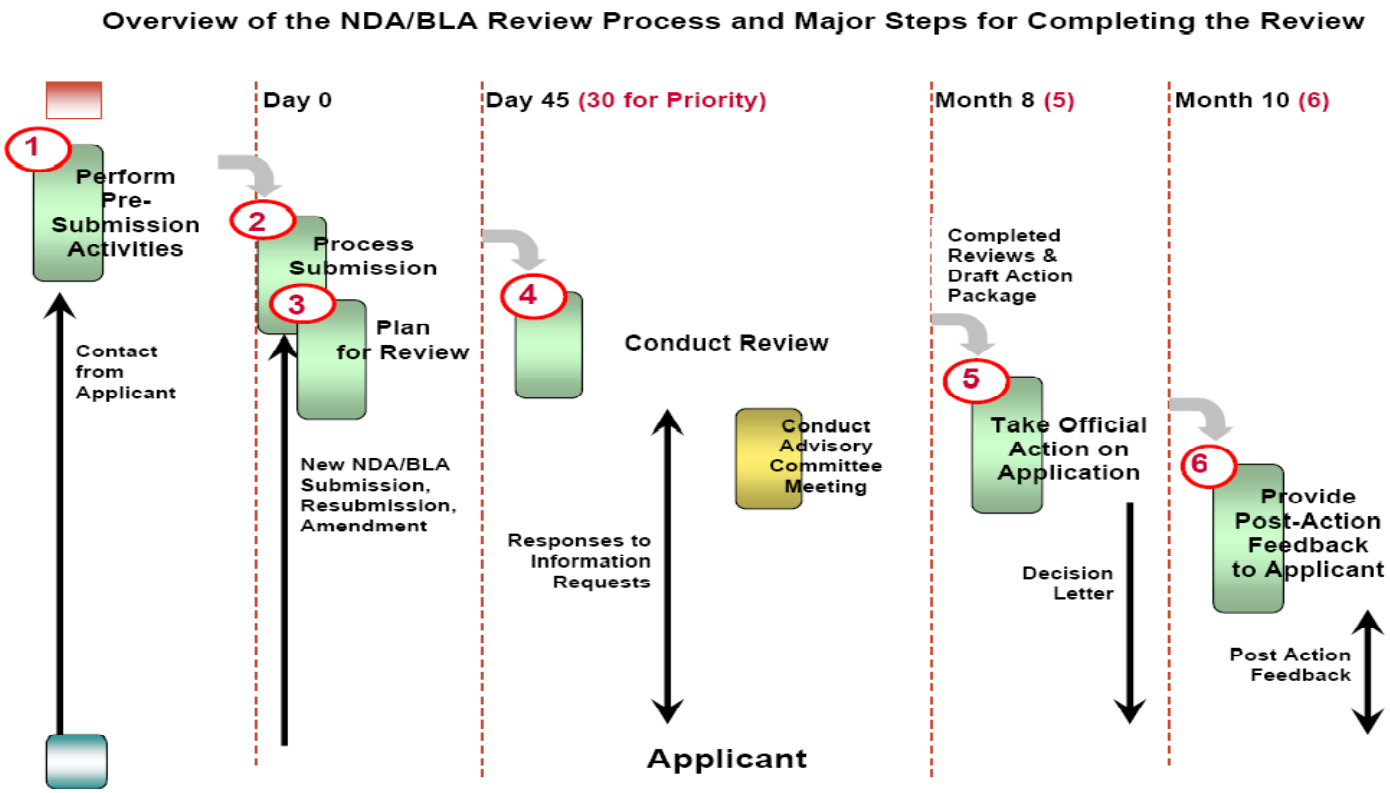
- Initial 30 day safety review
- Clinical responses
- Protocol reviews
- Clinical Study Reports
- Annual reports
- Safety reports
- Investigator Brochures
- Clinical Holds/Responses
- End Of Phase 1, 2, 3 Meetings
- Pre-NDA Meetings

NDA

- New application
- Supplements (efficacy, safety, pharmacology)
- Periodic Safety Update Reports

OTHERS: Meeting packages, consults

NDA Review Process



Sample Outline for NDA Clinical Review

1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS
1.1 Recommendation on Regulatory Action
1.2 Risk Benefit Analysis
1.3 Recommendations for Postmarket Risk Management Activities
1.4 Recommendations for Postmarket Studies/Clinical Trials
2. INTRODUCTION AND REGULATORY BACKGROUND
2.1 Product Information
2.2 Table(s) of Currently Available Treatment(s) for Proposed Indication(s)
2.3 Availability of Proposed Active Ingredient in the United States
2.4 Important Issues With Consideration to Related Drugs
2.5 Summary of Presubmission Regulatory Activity Related to Submission
2.6 Other Relevant Background Information
3. ETHICS AND GOOD CLINICAL PRACTICES
3.1 Submission Quality and Integrity
3.2 Compliance with Good Clinical Practices
3.3 Financial Disclosures
4 SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES
4.1 Chemistry Manufacturing and Controls
4.2 Clinical Microbiology
4.3 Preclinical Pharmacology/Toxicology
4.4 Clinical Pharmacology
4.4.1 Mechanism of Action
4.4.2 Pharmacodynamics
4.4.3 Pharmacokinetics
5 SOURCES OF CLINICAL DATA
5.1 Tables of Studies /Clinical Trials
5.2 Review Strategy
5.3 Discussion of Individual Studies/Clinical Trials
6. REVIEW OF EFFICACY
Efficacy Summary
6.1 Indication
6.1.1 Methods
6.1.2 Demographics
6.1.3 Subject Disposition
6.1.4 Analysis of Primary Endpoint(s)
6.1.5 Analysis of Secondary endpoint(s)
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects
6.1.10 Additional Efficacy Issues/Analyses
7. REVIEW OF SAFETY
Safety Summary
7.1 Methods
7.1.1 Studies/Clinical Trials Used to Evaluate Safety
7.1.3 Pooling Data Across Studies/Clinical trials to Estimate and Compare Incidence
7.2 Adequacy of Safety Assessments
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations
7.2.2 Explorations for Dose Response
7.2.3 Special Animal and/or In Vitro Testing
7.2.4 Routine Clinical Testing
7.2.5 Metabolic, Clearance, and Interaction Workup
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class
7.3 Major Safety Results and Discussion
7.3.2 Nonfatal Serious Adverse Events
7.3.3 Dropouts and/or Discontinuations
7.3.4 Significant Adverse Events
7.3.5 Submission Specific Primary Safety Concerns
7.4 Supportive Safety Results and Discussion
7.4.1 Common Adverse Events
7.4.2 Laboratory Findings
7.4.3 Vital Signs
7.4.4 Electrocardiograms (ECGs)
7.4.5 Special Safety Studies/Clinical trials
7.4.6 Immunogenicity
7.5 Other Safety Explorations
7.5.1 Dose Dependency for Adverse Findings
7.5.2 Time Dependency for Adverse Findings
7.5.3 Drug-Demographic Interactions (gender, race)
7.5.4 Drug Disease Interactions
7.5.5 Drug-Drug Interactions
7.6 Additional Safety Evaluations
7.6.1 Human Carcinogenicity
7.6.2 Human Reproduction and Pregnancy Data
7.6.3 Pediatrics and Assessment of Effects on Growth
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound
7.7 Additional Submissions
8. POSTMARKET EXPERIENCE
9. APPENDICES: 9.1 Literature Review /References
9.2 Labeling Recommendations
9.3 Advisory Committee Meeting

Bottom line…

- A clinical reviewer has a competing workload, compressed schedule

- A **quality** submission can make or break the review process
  - Electronic (eCTD) submission (i.e. no paper please!)
  - High quality big ticket items in the eCTD submission

Life before e-submissions…

http://www.circare.org/images/fda_ndaboxes.jpg

Big Ticket Clinical Modules

File Edit View Go Action Favorites Tools Help

Life Cycle

- 1. FDA Regional Information ← Module 1
  - 1.1. Forms
  - 1.2. Cover Letters
  - 1.3. Administrative Information
    - 1.3.3. Debarment Certification
    - 1.3.4. Financial Disclosure
    - 1.3.5. Patent Exclusivity
  - 1.4. Reference Section
  - 1.6. Meetings
  - 1.9. Pediatric Administrative Information
  - 1.11. Information Not Covered Under Modules 2 to 5
  - 1.12. Other Correspondence
  - 1.13. Annual Report
  - 1.14. Labeling
    - 1.14.1. Draft Labeling
    - 1.14.2. Final Labeling
  - 1.16. Risk Management Plans
- 2. Common Technical Document Summaries ← Module 2
  - 2.2. Introduction
  - 2.3. Quality Overall Summary
  - 2.4. Nonclinical Overview
  - 2.5. Clinical Overview
  - 2.6. Nonclinical Written and Tabulated Summaries
  - 2.7. Clinical Summary
- 3. Quality
- 4. Nonclinical Study Reports ← **Module 5**
- 5. Clinical Study Reports
  - 5.2. Tabular Listing of all Clinical Studies
  - 5.3.1. Reports of Biopharmaceutic Studies
  - 5.3.3. Reports of Human Pharmacokinetic (PK) Studies
  - 5.3.4. Reports of Human Pharmacodynamic (PD) Studies
  - 5.3.5. Reports of Efficacy and Safety Studies [Indication]
  - 5.3.6. Reports of Postmarketing Experience [Study ID - Title]
  - 5.4. Literature References

Life Cycle

Details | Annotations | Search | Print Queue | Dow

Revie...	Title
☐	Labeling

My Approach

- Big Ticket Folders:
  - Draft labeling
  - Clinical Summaries: Safety, Efficacy
  - Clinical Study Report (s)
  - Datasets
  - Integrated summaries of safety and efficacy

Aspects of Quality eCTD Submission

- Organization
- Format
- Bookmarks
- Hyperlinks
- Dataset size
- Dataset definitions

Organization

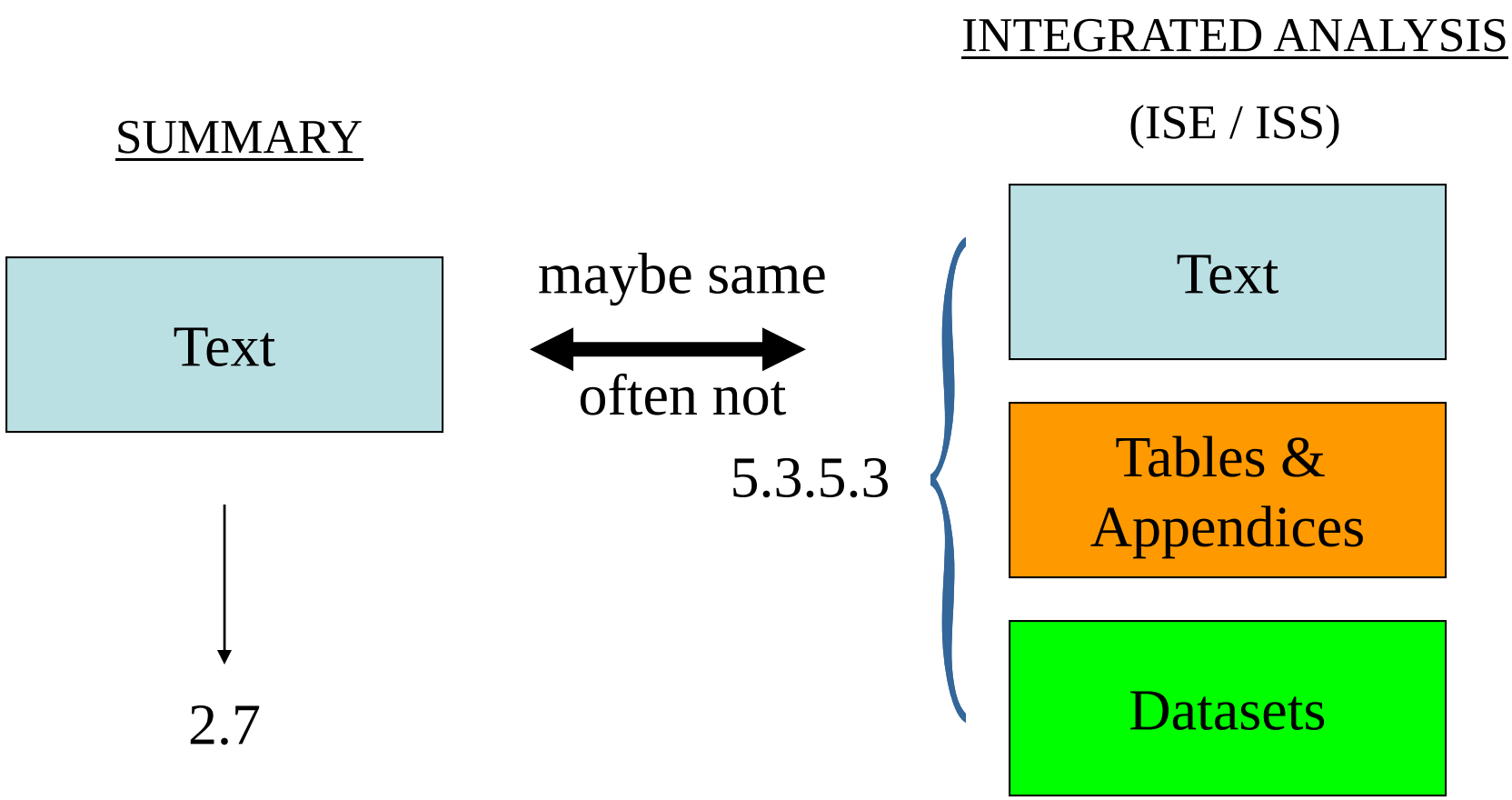
- Use “Comprehensive Table of Contents Headings and Hierarchy”
- Clinical Summary ≠ ISE, ISS
- Study Reports

Organization:
Clinical Summary vs. ISS/ISE

- Same: both are REQUIRED components in the eCTD in the U.S (21 CFR 314.50)

- Different:
  - Location within eCTD (Module 2 vs. Module 5)
  - Content (Summary vs. Integrated ANALYSIS)
  - Size (50-400 **text** pages vs. unlimited)

Clinical Summary vs. ISS/ISE con't..



Clinical summary vs. ISS/ISE con't…

- **Text** portion of ISS/ISE may be reused for clinical summary if it meets the requirements for a summary according to ICH M4E

(Hint: When writing the text portion of the ISE/ISS, use the headings for clinical summary of efficacy/safety)

Organization: Study Report

- If **one trial** for an indication contains controlled and uncontrolled studies, put them both in **one** place and not split them up in the controlled and uncontrolled study sections, respectively
- OR create a leaf in the uncontrolled section that refers back to the combined report

Organization: Study Report

- For legacy report, do not submit HUGE study files as a single pdf file
  (ideally keep file size **≤ 100 megabytes**)

- Break up report into main study report and appendices, etc.- stay at ICH granularity level, but not more granular (e.g., do not submit each case narrative as a single pdf file)

PDF Format

- Document content should be **text-based** as much as possible (avoid scanning in reports and including image-based items that can be converted into text)

Bookmarks

- Facilitate navigation
- Contained within Table of Contents
- Hyperlink to location in document
- Check to make sure Hyperlinks work

Bookmarks

HELPFUL

- 9 Investigational Plan
  - 9.1 Overall Study Design and Plan
  - 9.2 Rationale for Study Design and Control Group
  - 9.3 Selection of Study Population
  - 9.4 Treatments
  - 9.5 Efficacy and Safety Variables
  - 9.6 Data Quality Assurance
  - 9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size
  - 9.8 Changes in the Conduct of the Study or Planned Analyses
- 10 Study Patients
- 11 Efficacy Evaluation

NOT SO HELPFUL

13 DISCUSSION AND OVERALL CONCLUSIONS 77
14 TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT 78
15 REFERENCE LIST 79
16 APPENDICES 80

Hyperlinks

- Where:
  - Table of Contents
  - Throughout the body of the document
    - Related sections, references, appendices, tables, or figures not located on the same page

- Why: Improves navigation efficiency

Hyperlinks: References, Appendices

Week statistical safety report with combined [redacted] tables is provided in [Ref. 5.3.5.3: 923].

The clinical adverse experience profile including exposure-adjusted rates for patients in [redacted] summarized by treatment group including exposure-adjusted rates is presented in [Appendix 2.7.4: 30]. The number of patients with specific clinical

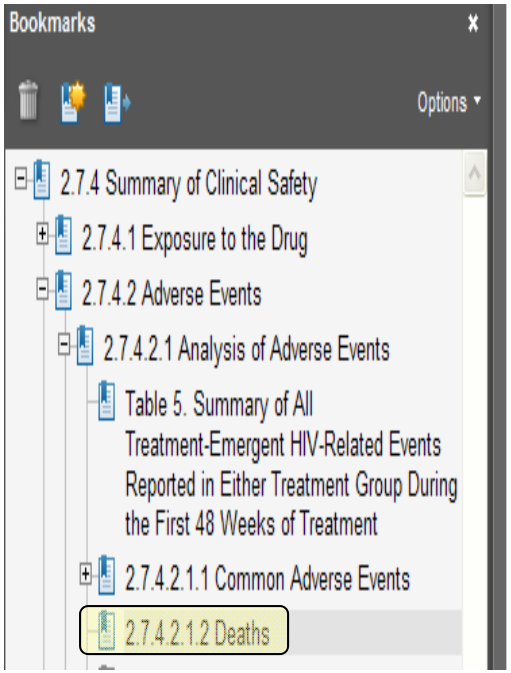
Hyperlinks: Source of summary information

Number of Patients n(%)			
Completed	214 (93.9%)	202 (86.7%)	416 (90.2%)
Discontinued	14 (6.1%)	31 (13.3%)	45 (9.8%)
Discontinuation due to:			
Adverse Event	6 (2.6%)	20 (8.6%)	26 (5.6%)
Protocol Violation	3 (1.3%)	2 (0.9%)	5 (1.1%)
Voluntary Withdrawal	4 (1.8%)	1 (0.4%)	5 (1.1%)
Lack of Efficacy	0 (0.0%)	2 (0.9%)	2 (0.4%)
Lost to Follow-up	0 (0.0%)	4 (1.7%)	4 (0.9%)
Investigator Recommendation	0 (0.0%)	1 (0.4%)	1 (0.2%)
Other	1 (0.4%)	1 (0.4%)	2 (0.4%)

Source: Table 14.1-2

Hyperlinks: Narratives

Helpful: Embed link within body of text



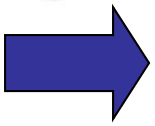
Narratives for subjects who died during the first 48 weeks are presented in the [redacted] 48-Week CSR, Section 14.3_3. A listing of deaths during the first 48 weeks is provided in [redacted]: Table 14.3_2.1 and Appendix 16.2_7.2.

2.7.4.2.1.3 Other Serious Adverse Events

A total of 28 (8.4%) QD-treated subjects and 36 (10.9%) BID-treated subjects experienced 1 or more treatment-emergent serious adverse events during the first 48 weeks of the study. Of these, 4 QD-treated subjects and 6 BID-treated subjects experienced 1 or more treatment-emergent serious adverse events that were considered

Hyperlinks: Narratives

Helpful: Organized by Death, Premature D/C, SAE



14.3__3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Narratives are provided for all fatal events, other serious adverse events considered probably related, possibly related, and probably not related to study drug by either the investigator [redacted] other significant adverse events, including hepatitis and body fat composition changes, and any adverse event leading to premature discontinuation.

Information included in the following subject narratives was obtained from data listings derived from the clinical database and may include additional information from the subject's safety file. Therefore, the narratives may contain additional information not available in the study tables.

Deaths-Subject Numbers

7033, 7244, 7336, 7608

Hepatitis-Subject Numbers

7138, 7607, 7618

Body Fat Composition Changes-Subject Numbers

7188, 7192, 7290, 7434, 7486, 7494, 7571, 7613, 7665

Premature Terminations-Subject Numbers

7028, 7051, 7068, 7082, 7111, 7116, 7137, 7206, 7214, 7230, 7232, 7249, 7275, 7285, 7456, 7501, 7539, 7570, 7594, 7609, 7653, 7655

Serious Adverse Events-Subject Numbers

7013, 7042, 7084, 7094, 7145, 7189, 7197, 7219, 7220, 7227, 7245, 7267, 7280, 7297, 7298, 7363, 7387, 7427, 7431, 7432, 7473, 7498, 7520, 7533, 7540, 7545, 7556, 7586, 7597, 7599, 7641

Hyperlinks: Other Useful Areas

- Case narratives → CRF
- Cases of lab outliers or special AEs → case narratives/CRF
- CRF: early withdrawal due to AE → AE information page

Hyperlinks: CRF early withdrawal page

End of Study Record
(Early Withdrawal)

Date of subject completion or discontinuation from the study [ ][ ] [ ][ ] [ ][ ]
day month year

Did the female partner of the male subject become pregnant during the study? ✔ *one:*

Not applicable [X] X (Female partner not of childbearing potential, or no female partner)

Yes [ ] Y *If YES, record details on PREGNANCY NOTIFICATION FORM.*

No [ ] N

✔ Did the subject discontinue the study prematurely? Yes [X] Y No [ ] N

*If YES, ✔ the **primary** reason for discontinuation. ✔ one:*

Adverse event [X] A *Record details on NON-SERIOUS ADVERSE EVENTS or SERIOUS ADVERSE EVENT page as appropriate.*

Consent withdrawn [ ] C

Lost to follow up [ ] L

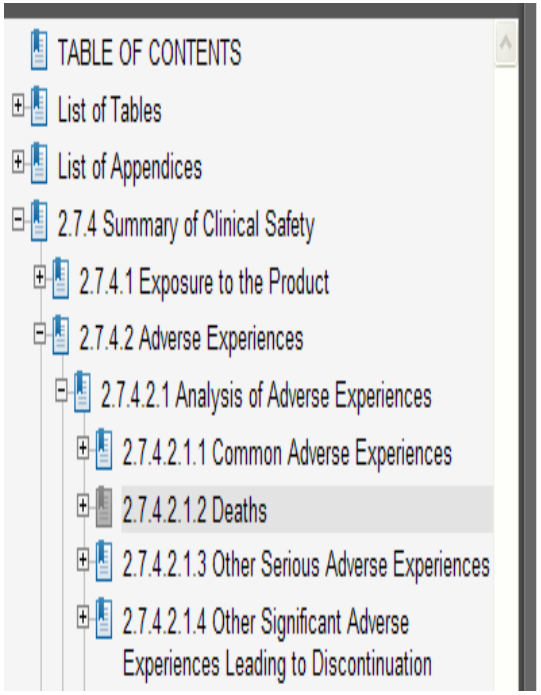
Protocol violation [ ] P

Lack of efficacy [ ] E

Other [ ] X *specify,* . . . . . .

Hyperlinks: Narratives

- Not Helpful: Link to Synopsis



2.7.4.2.1.2 Deaths

In addition to the review of fatal adverse experiences provided in this section, an analysis of mortality can be found in [Sec. 2.7.4.2.1.5.7]. Narratives for patients with adverse experiences resulting in death are provided in [Ref. 5.3.5.1: 370, 398, 615, 619, 733, [redacted]V3 [redacted]V3, [redacted]V2].

Reference 398

[redacted]Clinical Study Report (Synopsis), Multicenter Study: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Antiretroviral Activity of [redacted]

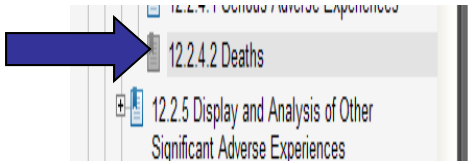
Hyperlinks: Narratives

- Not Helpful: Link to Clinical Study Report (p. 1), No Direct Link to Subject Narrative

2.7.4.2.1.2 Deaths

In addition to the review of fatal adverse experiences provided in this section, an analysis of mortality can be found in [Sec. 2.7.4.2.1.5.7]. Narratives for patients with adverse experiences resulting in death are provided in [Ref. 5.3.5.1: 370, 398, 615, 619, 733, [redacted] V3, [redacted] V3, [redacted] V2].

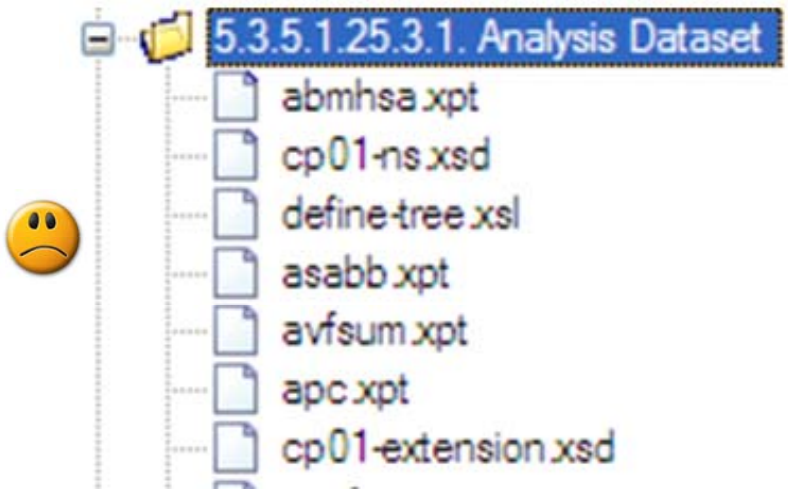
Takes you to p.1 CSR -> Find Deaths in TOC -> Click on Hyperlink to find:

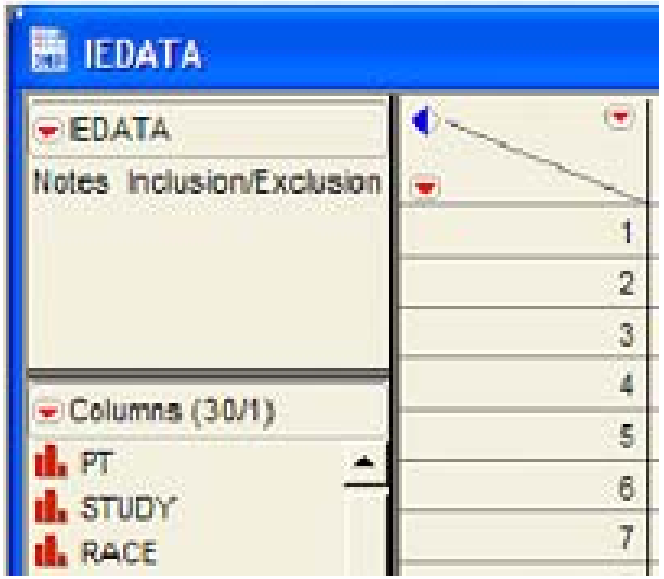


the [redacted] was considered to be in the post-study phase. Additional information regarding these deaths can be found on the medium [redacted] report [16.2.7.1] and death narratives (provided in Section 14.5).

Dataset Definitions

- Define datasets
- Select user-friendly dataset names
- Easy to access dataset definition





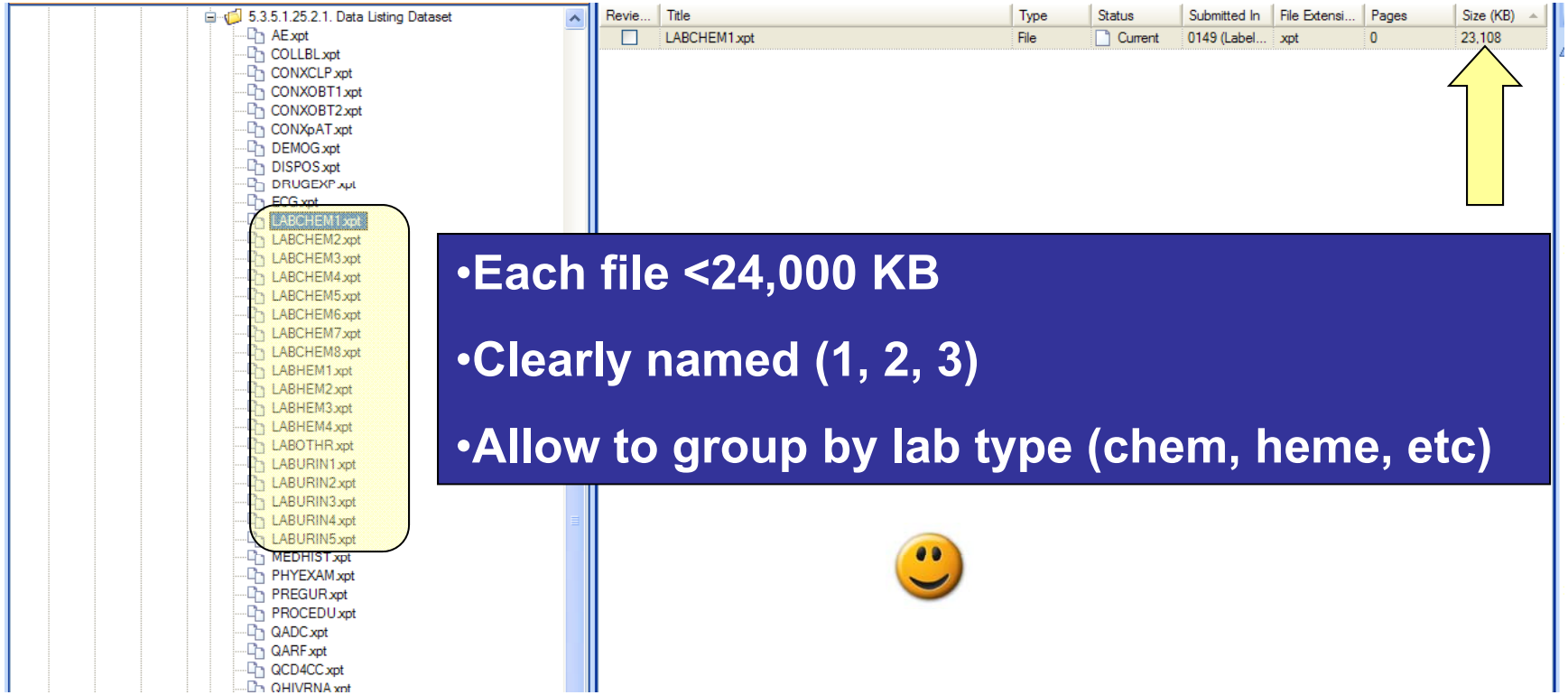
Need for Clarification takes Time Away from Review

Dataset Size

- Dataset files should be generally < 400 MB per file

- We recommend discussion of data requirements with the review division prior to submitting

Dataset Size: Smaller Files



- Each file <24,000 KB
- Clearly named (1, 2, 3)
- Allow to group by lab type (chem, heme, etc)

Conclusion

- eCTD format simplifies the review process
  - Clinical reviewers have competing priorities and established timelines
- Appropriate organization, format, bookmarks, hyperlinks and dataset submissions maximize eCTD usefulness

Thank You!