eCTD: A Clinical Reviewer's Experience

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Disclaimer

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Outline

- My Perspective
- NDA Review Process
- EDR/eCTD Viewer
- Elements of Submission - Examples
  - Organization
  - Format
    - Bookmarks
    - Hyperlinks
  - Datasets

My Typical Workload

- Primarily review INDs and NDAs
- Responsible for 27 INDs and 3 NDAs

IND

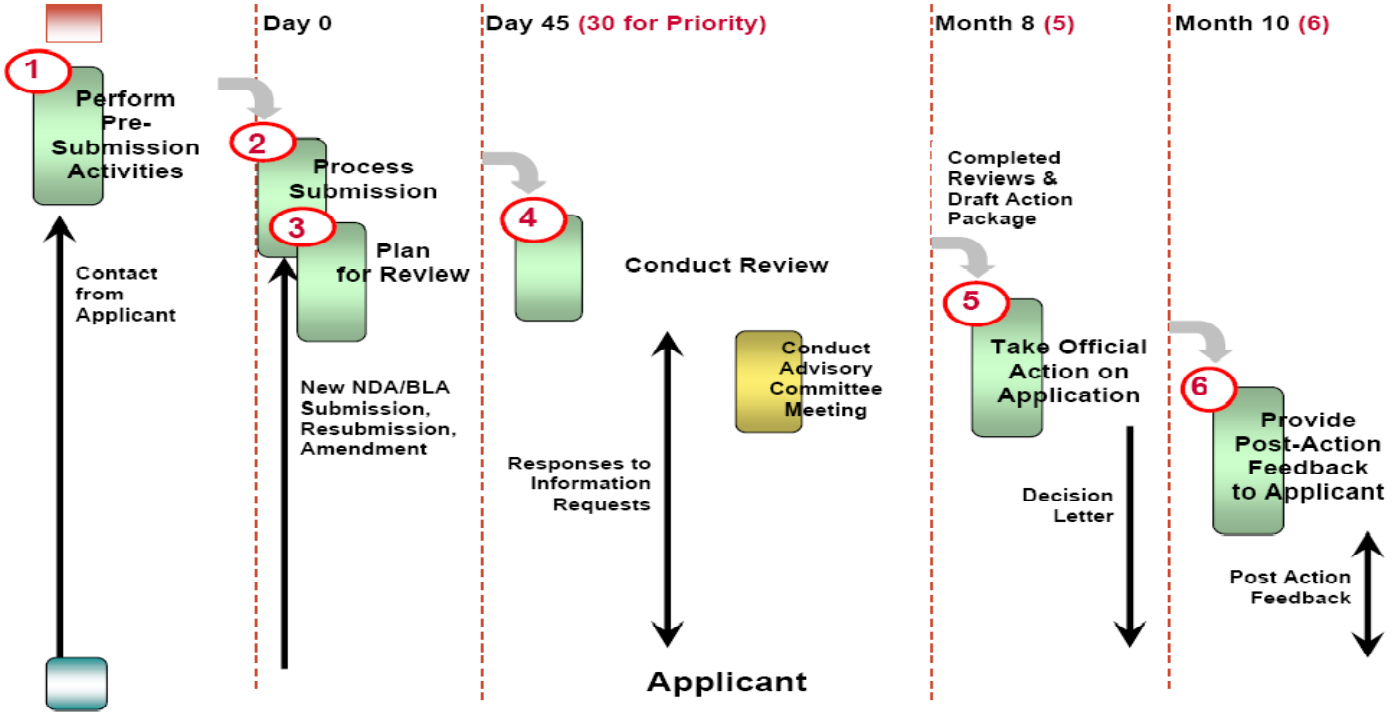
- Initial 30 day safety review
- Clinical responses
- Protocol reviews
- Clinical Study Reports
- Annual reports
- Safety reports
- Investigator Brochures
- Clinical Holds/Responses
- End Of Phase 1, 2, 3 Meetings
- Pre-NDA Meetings

NDA

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

NDA Review Process

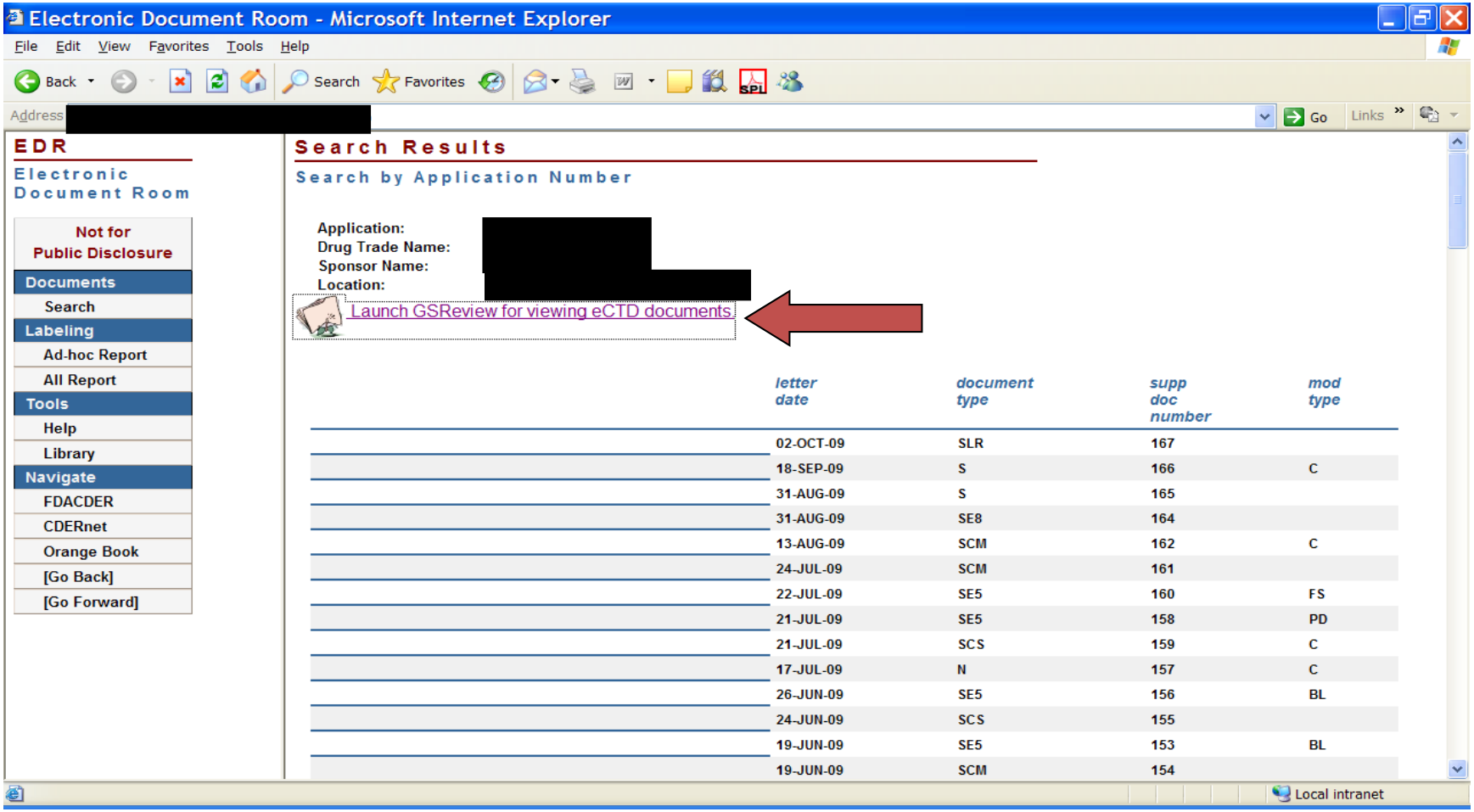
Overview of the NDA/BLA Review Process and Major Steps for Completing the Review



Life before e-submissions…

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

Access using EDR



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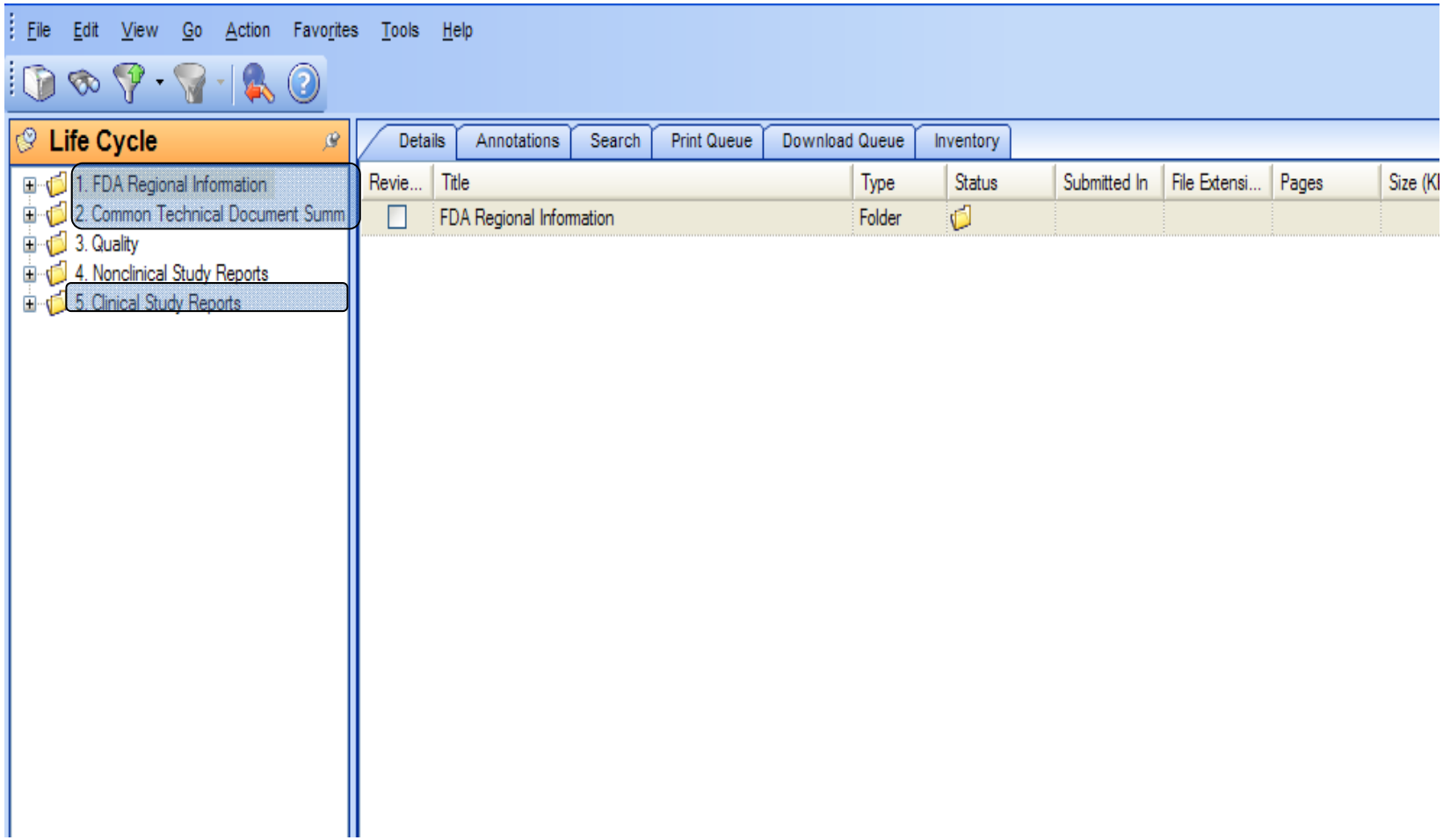
31-AUG-09	S	165	
31-AUG-09	SE8	164	
13-AUG-09	SCM	162	C
24-JUL-09	SCM	161	
22-JUL-09	SE5	160	FS
21-JUL-09	SE5	158	PD
21-JUL-09	SCS	159	C
17-JUL-09	N	157	C
26-JUN-09	SE5	156	BL
24-JUN-09	SCS	155	
19-JUN-09	SE5	153	BL
19-JUN-09	SCM	154	

eCTD Viewer


File Edit View Go Action Favorites Tools Help
Life Cycle
1. FDA Regional Information
2. Common Technical Document Summ
3. Quality
4. Nonclinical Study Reports
5. Clinical Study Reports
Details
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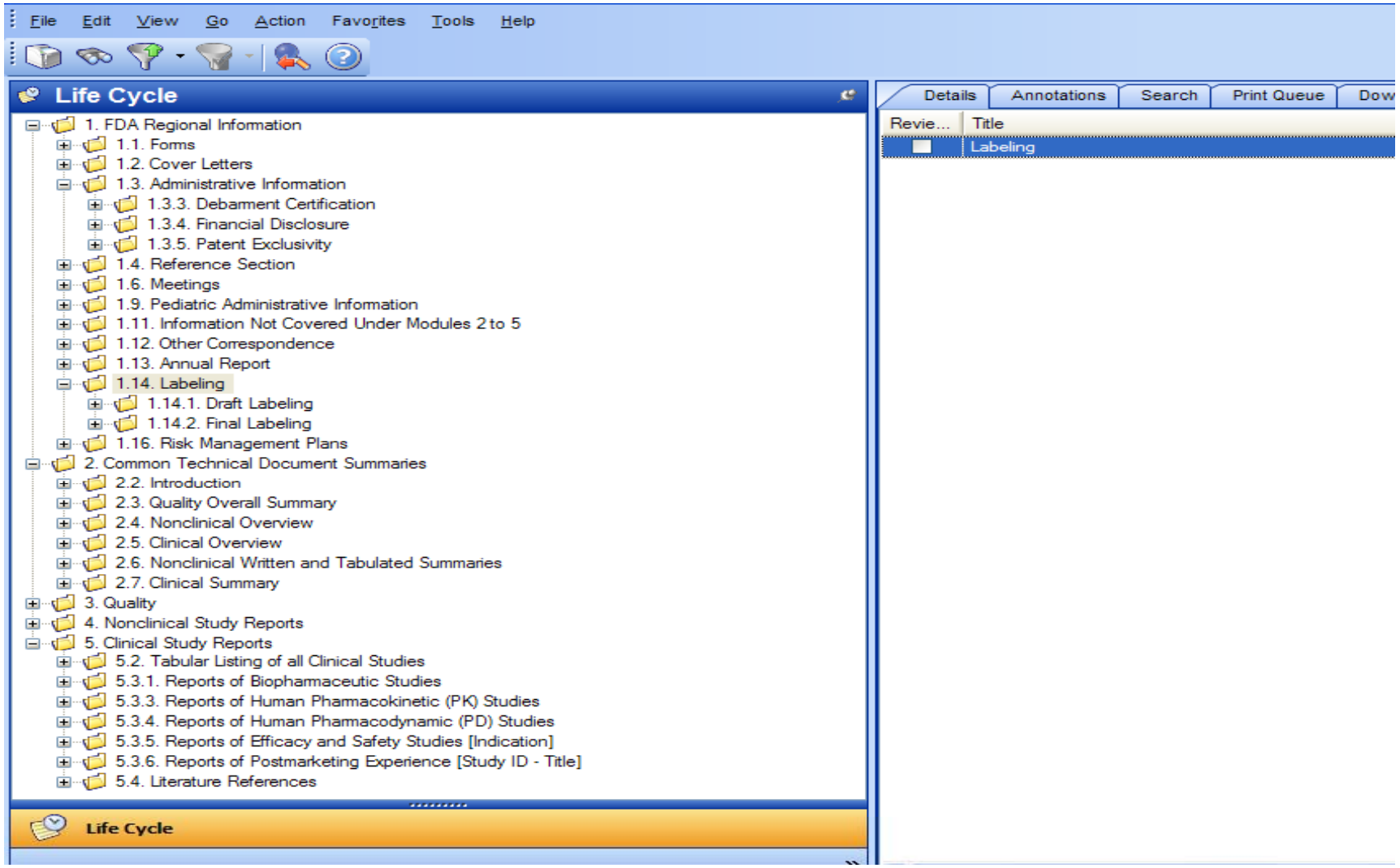
My Focus in eCTD Viewer



Sample Outline for NDA Clinical Review

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT
1.1 Recommendation on Regulatory Action
1.2 Risk Benefit Assessment
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies
1.4 Recommendations for Postmarket Requirements and Commitments

2 INTRODUCTION AND REGULATORY BACKGROUND
2.1 Product Information
2.2 Tables of Currently Available Treatments for Proposed Indications
2.3 Availability of Proposed Active Ingredient in the United States
2.4 Important Safety 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/SAFETY ISSUES 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 Endpoints(s)
6.1.6 Other Endpoints
6.1.7 Subpopulations
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
7.1.2 Categorization of Adverse Events
7.1.3 Pooling of 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
7.3.1 Deaths
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
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 Events
7.5.2 Time Dependency for Adverse Events
7.5.3 Drug-Demographic Interactions
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 / Safety Issues

8 POSTMARKET EXPERIENCE

9 APPENDICES
9.1 Literature Review/References
9.2 Labeling Recommendations
9.3 Advisory Committee Meeting

My Approach

- **Big Ticket Folders:**
  - **Clinical Summary: Safety, Efficacy**
  - **Draft Labeling**
  - **ISE/ISS**
  - **Clinical Study Report(s)**
  - **Datasets and Dataset Definitions**

- **Competing Workload + Compressed Schedule → High Quality eCTD submissions Help review process**

Goal

- **Translate efficacy and safety data into a comprehensive review and label**
- **Understand how key analyses performed**
- **Perform confirmatory and individualized exploratory analyses as appropriate**
- **Minimize time spent on:**
  - **searching for supportive data**
  - **decoding datasets**
  - **rectifying discordant Sponsor/Reviewer results**

Aspects of High Quality eCTD Submission

- **Organization**
- **Format**
  - **Table of Contents**
  - **Bookmarks**
  - **Hyperlinks**
- **Datasets**

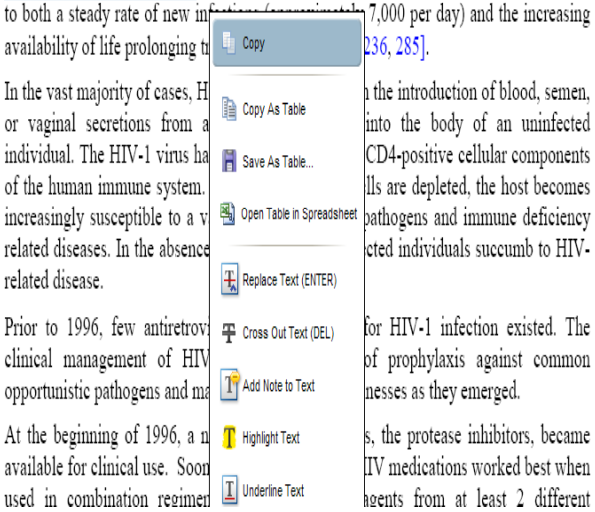
Organization

- **Use "Comprehensive Table of Contents Headings and Hierarchy"**

- **Clinical Summary ≠ ISE, ISS**
  - **April 2009 Guidance**
  - **"ISE and ISS are required in applications submitted to the FDA in accordance with the regulations for NDA submissions"**
    - **(21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a))**
  - **"clinical summary sections should not be considered the appropriate location for the ISE or ISS, with rare exceptions."**

PDF in appropriate format

Help



2.5.1.4 Scientific Background and Introduction

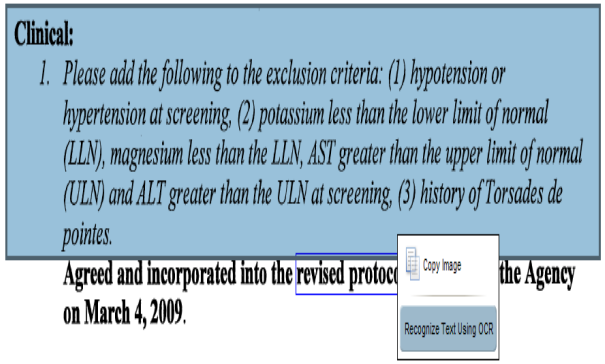
Human Immunodeficiency virus type 1 (HIV-1) is the virus that causes the Acquired Immune Deficiency Syndrome (AIDS). An estimated 33 million people are infected with HIV-1 worldwide as of 2007 [Ref. 5.4: 625]. The prevalence of HIV is rising secondary to both a steady rate of new in 7,000 per day) and the increasing availability of life prolonging t 236, 285].

In the vast majority of cases, H the introduction of blood, semen, or vaginal secretions from a into the body of an uninfected individual. The HIV-1 virus ha CD4-positive cellular components of the human immune system. lls are depleted, the host becomes increasingly susceptible to a v pathogens and immune deficiency related diseases. In the absence cted individuals succumb to HIV-related disease.

Prior to 1996, few antiretrov for HIV-1 infection existed. The clinical management of HIV of prophylaxis against common opportunistic pathogens and ma nesses as they emerged.

At the beginning of 1996, a n s, the protease inhibitors, became available for clinical use. Soon IV medications worked best when used in combination regimen agents from at least 2 different

Hindrance



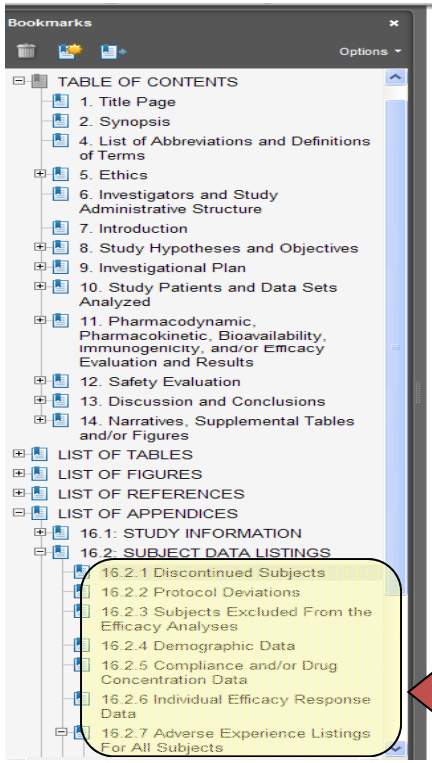
Clinical:

1. *Please add the following to the exclusion criteria: (1) hypotension or hypertension at screening, (2) potassium less than the lower limit of normal (LLN), magnesium less than the LLN, AST greater than the upper limit of normal (ULN) and ALT greater than the ULN at screening, (3) history of Torsades de pointes.*

Agreed and incorporated into the revised protoc the Agency on March 4, 2009.

Bookmarks

- Contained within Table of Contents
- Hyperlink to the Reference
- Check to make sure Hyperlinks work



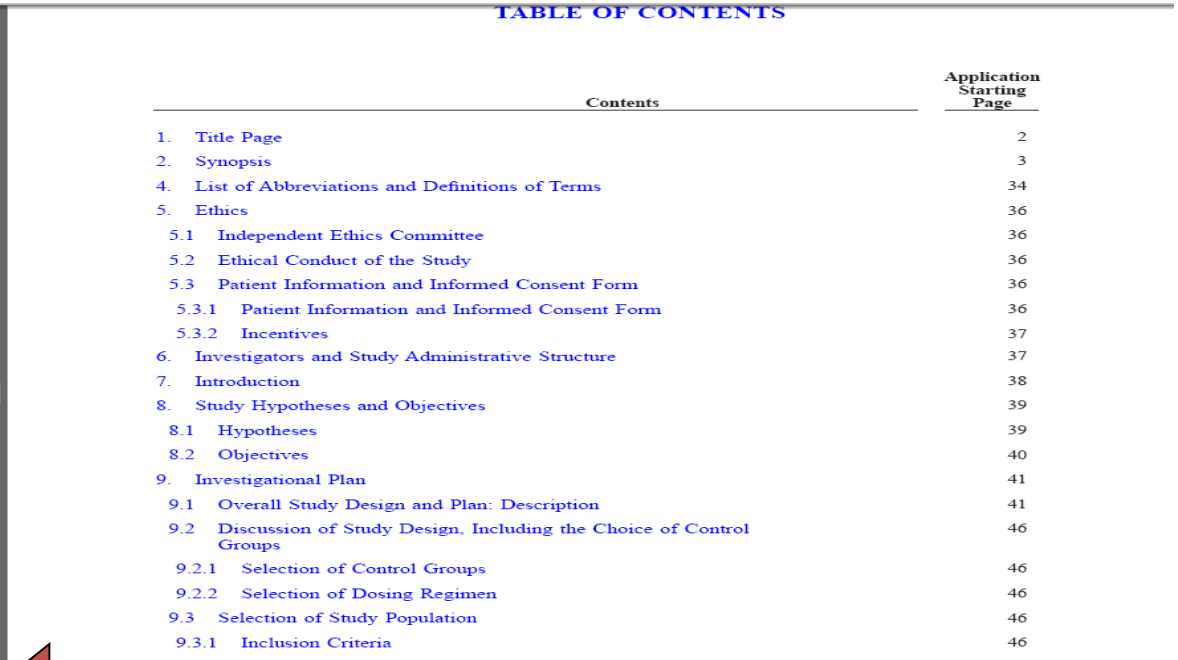


TABLE OF CONTENTS

Hyperlinks

- **Where:** **Table of Contents**
  Throughout the body of the document
  - » **Related sections, references, appendices, tables, or figures not located on same page**
- **Why:** **Improves navigation efficiency**
- **Refer to PDF Specification and eCTD Guidance**

PDF Specification:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf
eCTD Guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf

Hyperlinks: Data Source

Patient Status by Treatment Group

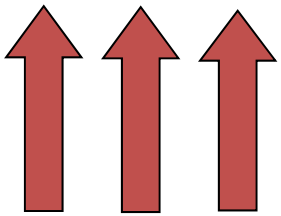
	[redacted]		Total
	n (%)	n (%)	n (%)
Total Enter	177 (100)	175 (100)	352 (100)
Never Treated	3 (1.7)	1 (0.6)	4 (1.1)
Treated	174 (98.3)	174 (99.4)	348 (98.9)
Discontinued study	25 (14.1)	17 (9.7)	42 (11.9)
Lack of efficacy	3 (1.7)	1 (0.6)	4 (1.1)
Adverse experience	7 (4.0)	3 (1.7)	10 (2.8)
Withdrew consent	9 (5.1)	6 (3.4)	15 (4.3)
Lost to follow-up	0 (0.0)	4 (2.3)	4 (1.1)
Deviation from protocol	1 (0.6)	1 (0.6)	2 (0.6)
Physician decision	4 (2.3)	2 (1.1)	6 (1.7)
Other[†]	1 (0.6)	0 (0.0)	1 (0.3)

[†]Including patients who moved or relocated, pregnant, with progressive disease, or the clinical trial was terminated at the site.

[redacted]

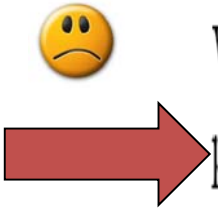
n (%)= Number (percent) of patients in each sub-category.

Data Source: [16.4.1.1; 16.4.3.3; 16.4.5.2]



Hyperlink takes me to Page 1 of the 156 page Define.XML file

Hyperlinks
References, Appendices

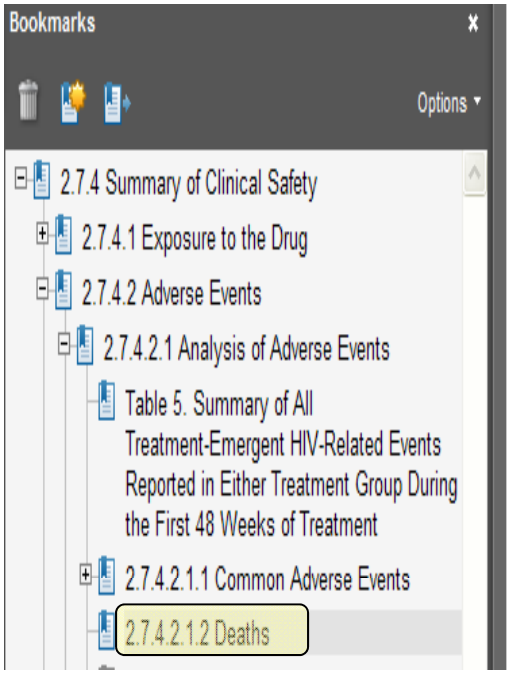


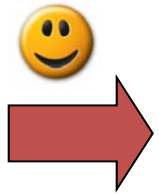
Week statistical safety report with combined [redacted] tables is provided in [Ref. 5.3.5.3: 923].

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: Narratives

Helpful: Embed link within body of text





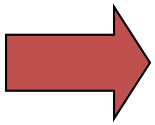
Narratives for subjects who died during the first 48 weeks are presented in the [redacted] 48-Week CSR, Section 14.3_3. A listing of deaths during the first 48 weeks is provided in [redacted] Table 14.3_2.1 and Appendix 16.2_7.2.

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

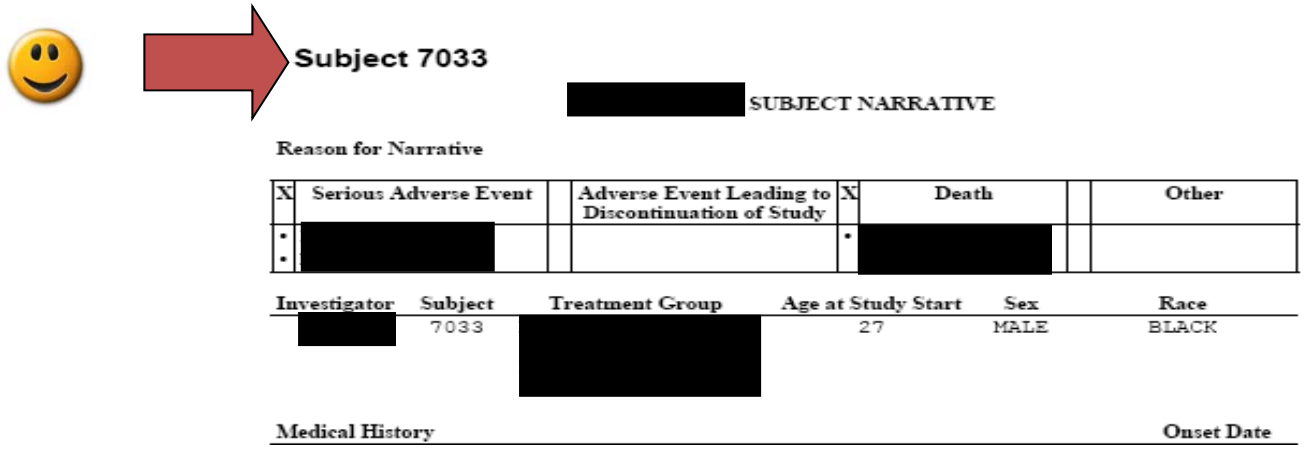
7028, 7051, 7068, 7082, 7111, 7116, 7137, 7206, 7214, 7230, 7232, 7249, 7275, 7285, 7456, 7501, 7539, 7570, 7594, 7609, 7653, 7655

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: Narratives

- **Helpful: Link directly with Subject Narrative**



Subject 7033

[redacted] SUBJECT NARRATIVE

Reason for Narrative

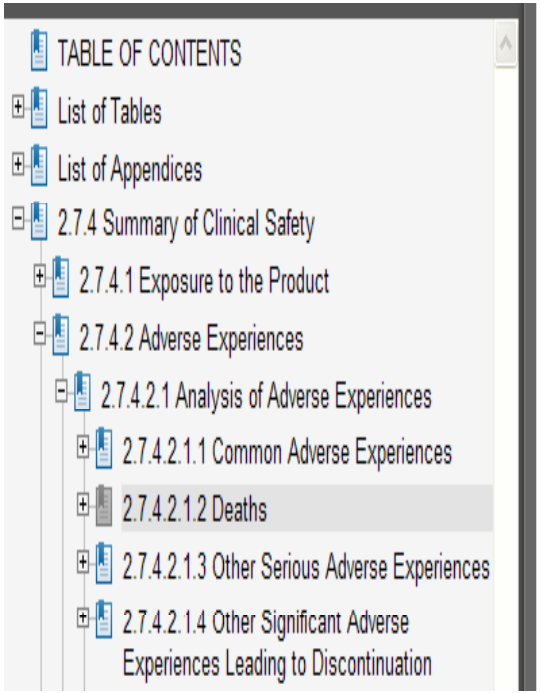
X	Serious Adverse Event		Adverse Event Leading to Discontinuation of Study	X	Death		Other
•	[redacted]			•	[redacted]		

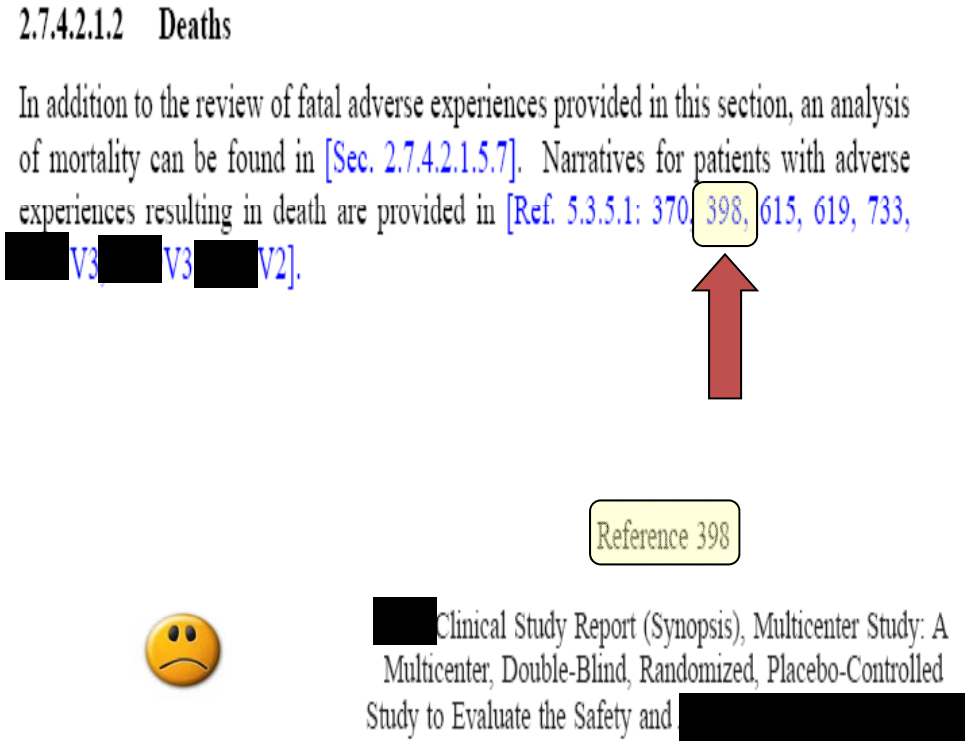
Investigator	Subject	Treatment Group	Age at Study Start	Sex	Race
[redacted]	7033	[redacted]	27	MALE	BLACK

Medical History — Onset Date

Hyperlinks: Narratives

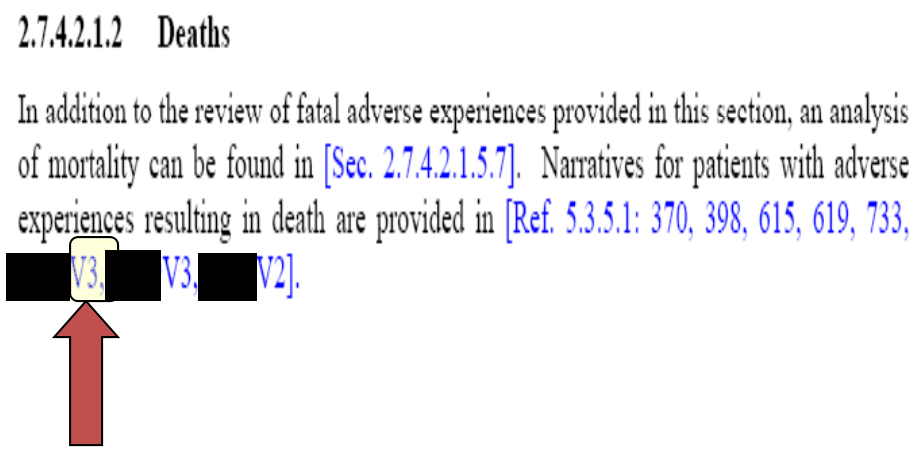
- **Not Helpful: Link to <u>Synopsis</u>**



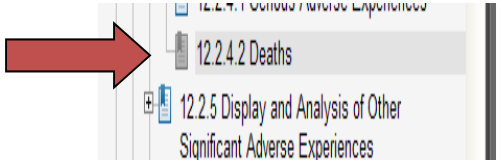


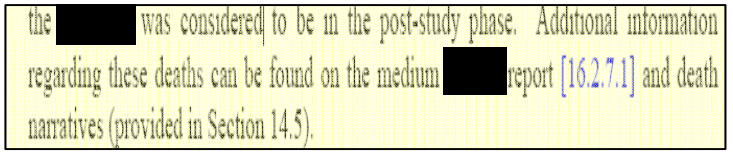
Hyperlinks: Narratives

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



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





Dataset Definitions

Definitions not provided

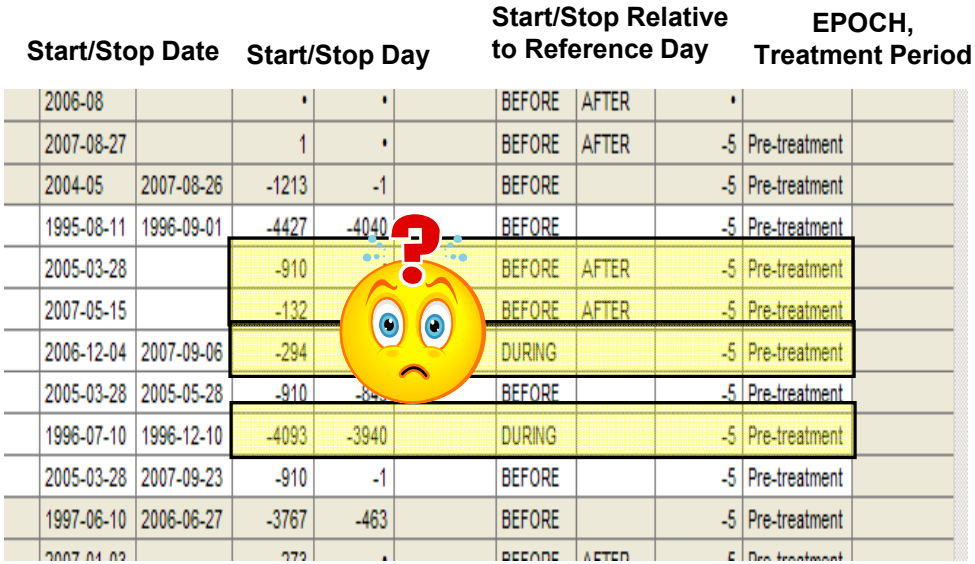
FDA Query:

4. Please let us know where we can locate the definitions for:

Post Viral Fail Max
Post-Treatment PVFM
Post-Treatment PVFO
Post Viral Fail Optm

[redacted]esponse:

We apologize that the treatment phase definitions were not provided with the [redacted] datasets. The definitions are as follows:



Start/Stop Date		Start/Stop Day			Start/Stop Relative to Reference Day		EPOCH, Treatment Period	
2006-08					BEFORE	AFTER		
2007-08-27		1			BEFORE	AFTER	-5	Pre-treatment
2004-05	2007-08-26	-1213	-1		BEFORE		-5	Pre-treatment
1995-08-11	1996-09-01	-4427	-4040		BEFORE		-5	Pre-treatment
2005-03-28		-910			BEFORE	AFTER	-5	Pre-treatment
2007-05-15		-132			BEFORE	AFTER	-5	Pre-treatment
2006-12-04	2007-09-06	-294			DURING		-5	Pre-treatment
2005-03-28	2005-05-28	-910	-84		BEFORE		-5	Pre-treatment
1996-07-10	1996-12-10	-4093	-3940		DURING		-5	Pre-treatment
2005-03-28	2007-09-23	-910	-1		BEFORE		-5	Pre-treatment
1997-06-10	2006-06-27	-3767	-463		BEFORE		-5	Pre-treatment
2007-01-03		273			BEFORE	AFTER		Pre-treatment

Concomitant Medications

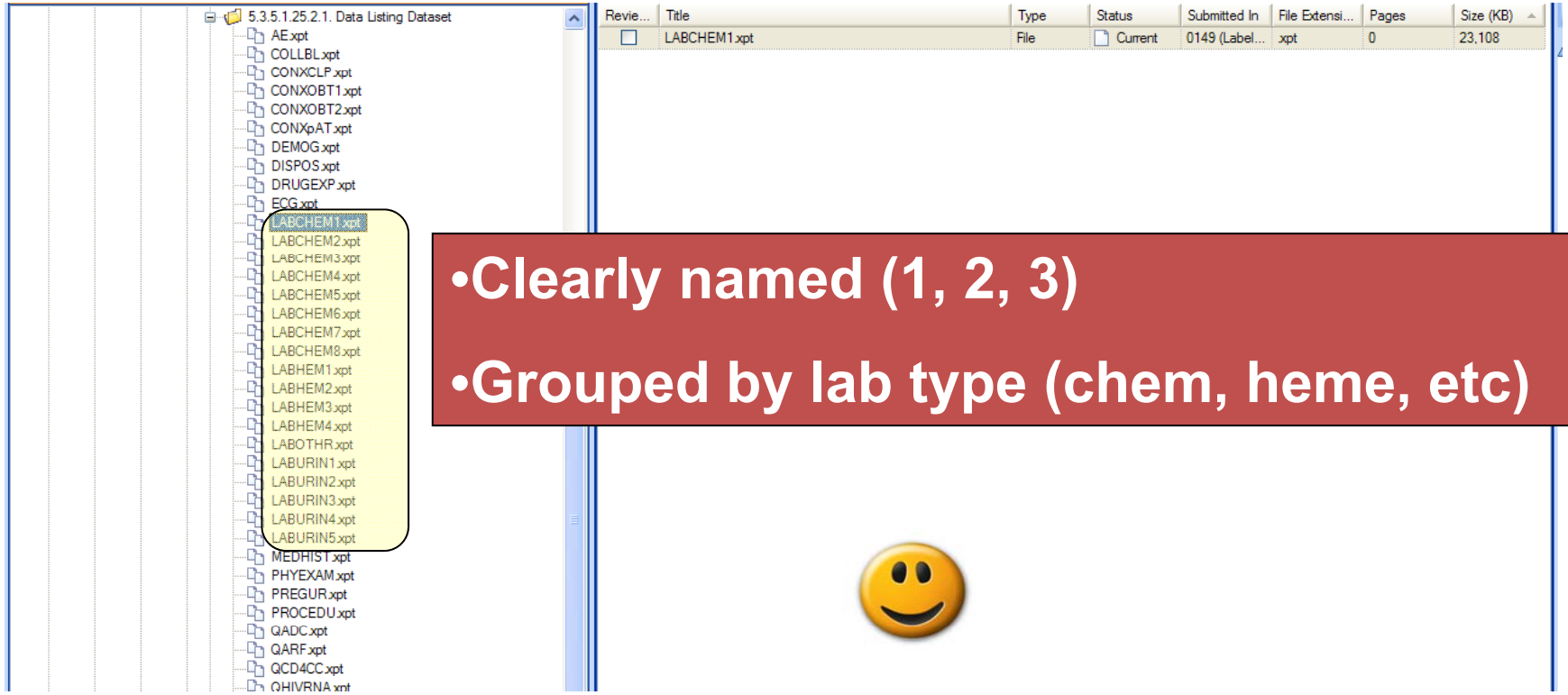
Need for Clarification takes Time Away from Review

Dataset Size

- **Non SDTM dataset files should be generally <400 MB per file**

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

Dataset Files



- Clearly named (1, 2, 3)
- Grouped by lab type (chem, heme, etc)

Summary

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