

eCTD: A Clinical Reviewer's Experience

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FDA

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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

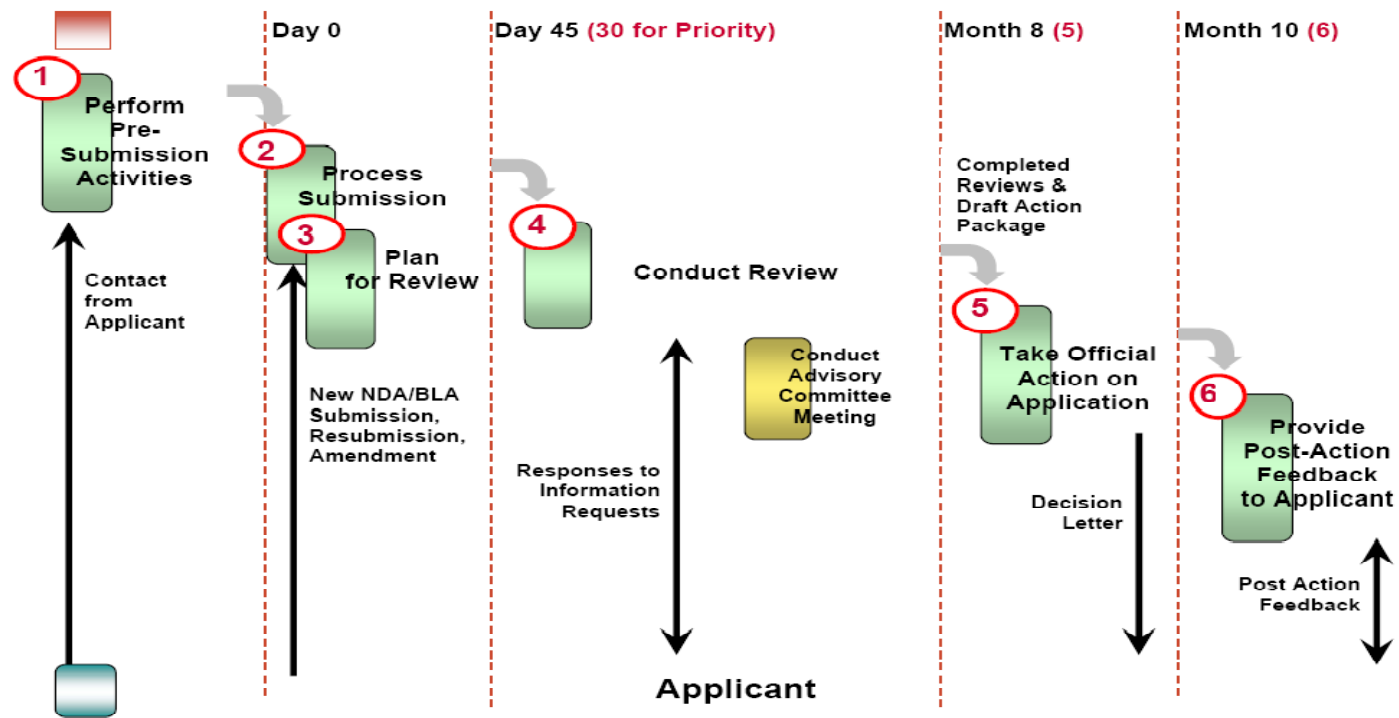
NDA

- 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



Electronic Document Room - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites

Address [Redacted]

EDR
Electronic Document Room

- Not for Public Disclosure
- Documents
- Search
- Labeling
- Ad-hoc Report
- All Report
- Tools
- Help
- Library
- Navigate
- FDACDER
- CDERnet
- Orange Book
- [Go Back]
- [Go Forward]

Search Results
Search by Application Number

Application: [Redacted]
Drug Trade Name: [Redacted]
Sponsor Name: [Redacted]
Location: [Redacted]

[Launch GSReview for viewing eCTD documents](#)

<i>letter date</i>	<i>document type</i>	<i>supp doc number</i>	<i>mod type</i>
02-OCT-09	SLR	167	
18-SEP-09	S	166	C
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	

Local intranet

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 Annotations Search Print Queue Download Queue Inventory

Revie...	Title	Type	Status	Submitted In	File Extensi...	Pages	Size (KI
<input type="checkbox"/>	FDA Regional Information	Folder					

My Focus in eCTD Viewer



The screenshot displays the eCTD Viewer application interface. At the top, there is a menu bar with options: File, Edit, View, Go, Action, Favorites, Tools, and Help. Below the menu is a toolbar with various icons for navigation and search. The main area is divided into two panes. The left pane, titled "Life Cycle", contains a hierarchical tree view of document sections. The right pane, titled "Details", shows a table with columns "Review..." and "Title".

Life Cycle Tree View:

- 1. FDA Regional Information
 - 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
 - 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
- 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

Details Pane Table:

Review...	Title
<input type="checkbox"/>	Labeling

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.”**

Bookmarks



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

Bookmarks

- TABLE OF CONTENTS
 - 1. Title Page
 - 2. Synopsis
 - 4. List of Abbreviations and Definitions of Terms
 - 5. Ethics
 - 6. Investigators and Study Administrative Structure
 - 7. Introduction
 - 8. Study Hypotheses and Objectives
 - 9. Investigational Plan
 - 10. Study Patients and Data Sets Analyzed
 - 11. Pharmacodynamic, Pharmacokinetic, Bioavailability, Immunogenicity, and/or Efficacy Evaluation and Results
 - 12. Safety Evaluation
 - 13. Discussion and Conclusions
 - 14. Narratives, Supplemental Tables and/or Figures
- LIST OF TABLES
- LIST OF FIGURES
- LIST OF REFERENCES
- LIST OF APPENDICES
- 16.1: STUDY INFORMATION
- 16.2: SUBJECT DATA LISTINGS
 - 16.2.1 Discontinued Subjects
 - 16.2.2 Protocol Deviations
 - 16.2.3 Subjects Excluded From the Efficacy Analyses
 - 16.2.4 Demographic Data
 - 16.2.5 Compliance and/or Drug Concentration Data
 - 16.2.6 Individual Efficacy Response Data
 - 16.2.7 Adverse Experience Listings For All Subjects

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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

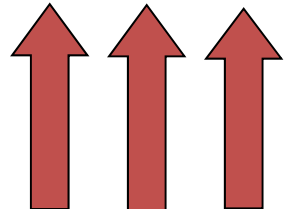
	[REDACTED]		Total
	n (%)	n (%)	n (%)
Total Enter	177 (100)	175 (100)	352 (100)
Never Treated	3 (1.7)	1 (0.6)	4 (1.1)
Treated	174 (98.3)	174 (99.4)	348 (98.9)
Discontinued study	25 (14.1)	17 (9.7)	42 (11.9)
Lack of efficacy	3 (1.7)	1 (0.6)	4 (1.1)
Adverse experience	7 (4.0)	3 (1.7)	10 (2.8)
Withdrew consent	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: [16411](#) · [16433](#) · [16452](#)



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

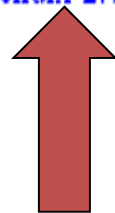
Hyperlinks

References, Appendices



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

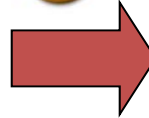
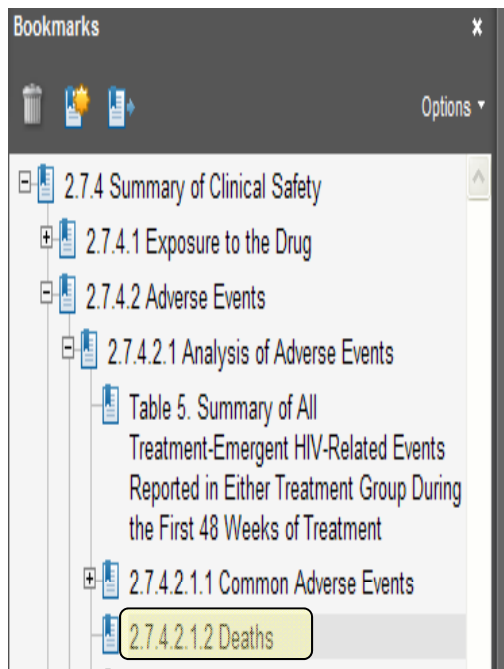
The clinical adverse experience profile including exposure-adjusted rates for patients in [REDACTED] summarized by treatment group including exposure-adjusted rates is presented in [\[Appendix 2.7.4: 30\]](#). The number of patients with specific clinical



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

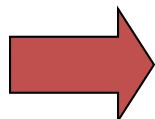


Helpful: Organized by Death, Premature D/C, SAE

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](#)

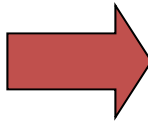
Serious Adverse Events-Subject Numbers

[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

██████████ SUBJECT NARRATIVE

Reason for Narrative

<input checked="" type="checkbox"/>	Serious Adverse Event	Adverse Event Leading to Discontinuation of Study	<input checked="" type="checkbox"/>	Death		Other
<input checked="" type="checkbox"/>	██████████		<input checked="" type="checkbox"/>	██████████		

Investigator	Subject	Treatment Group	Age at Study Start	Sex	Race
██████████	7033	██████████	27	MALE	BLACK

Medical History

Onset Date

Hyperlinks: Narratives



- **Not Helpful: Link to Synopsis**

- TABLE OF CONTENTS
- List of Tables
- List of Appendices
- 2.7.4 Summary of Clinical Safety
 - 2.7.4.1 Exposure to the Product
 - 2.7.4.2 Adverse Experiences
 - 2.7.4.2.1 Analysis of Adverse Experiences
 - 2.7.4.2.1.1 Common Adverse Experiences
 - 2.7.4.2.1.2 Deaths
 - 2.7.4.2.1.3 Other Serious Adverse Experiences
 - 2.7.4.2.1.4 Other Significant Adverse Experiences Leading to Discontinuation

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 [REDACTED]

Hyperlinks: Narratives



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

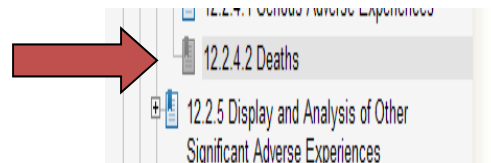
2.7.4.2.1.2 Deaths

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,

██████ V3, ██████ V3, ██████ V2].



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



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



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

response:

We apologize that the treatment phase definitions were not provided with the 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 -854	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
2007-04-02	272	BEFORE AFTER	5 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



5.3.5.1.25.2.1. Data Listing Dataset

- AE.xpt
- COLLBL.xpt
- CONXCLP.xpt
- CONXOBT1.xpt
- CONXOBT2.xpt
- CONXPAT.xpt
- DEMOG.xpt
- DISPOS.xpt
- DRUGEXP.xpt
- ECG.xpt
- LABCHEM1.xpt**
- LABCHEM2.xpt
- LABCHEM3.xpt
- LABCHEM4.xpt
- LABCHEM5.xpt
- LABCHEM6.xpt
- LABCHEM7.xpt
- LABCHEM8.xpt
- LABHEM1.xpt
- LABHEM2.xpt
- LABHEM3.xpt
- LABHEM4.xpt
- LABOTHR.xpt
- LABURIN1.xpt
- LABURIN2.xpt
- LABURIN3.xpt
- LABURIN4.xpt
- LABURIN5.xpt
- MEDHIST.xpt
- PHYEXAM.xpt
- PREGUR.xpt
- PROCEU.xpt
- QADC.xpt
- QARF.xpt
- QCD4CC.xpt
- QHVRNA.xpt

Revie...	Title	Type	Status	Submitted In	File Extensi...	Pages	Size (KB)
<input type="checkbox"/>	LABCHEM1.xpt	File	<input type="checkbox"/> Current	0149 (Label...	.xpt	0	23,108

- 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**

