Experiences in Preparing OSI Deliverables for US sBLA Filing

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Nov 3th, 2017

Outline

- **Office of Scientific Investigations (OSI)**
- Case Study
  - Inspection of Study Sites and Information Request
  - How OSI Request is Handled
- Some Considerations
- Final Remarks

Office of Scientific Investigations

- The goals of the **Office of Scientific Investigations (OSI)** are to verify the integrity of efficacy and safety data submitted to the FDA in support of new drug applications and to assure that the rights and welfare of human research subjects are protected.
- For NDAs and BLAs submitted to CDER (as well as supplemental application for each), the OSI has responsibility for **on-site inspection planning**:
  - Select sites for inspection
  - Generate inspectional assignments
  - Generate background packages that office of regulatory affairs (ORA) investigators need to conduct inspections
- See the **the OSI Homepage** for further information

About the Center for Drug Evaluation and Research

- CDER Offices and Divisions
- Drug Safety Oversight Board
- Jobs at the Center for Drug Evaluation and Research (CDER)
- Meeting Presentations (Drugs)
- CDER Exclusivity Board
- Jobs at the Center for Drug Evaluation and Research
- FAQs about CDER
- Reports & Budgets (CDER)
- Manual of Policies & Procedures (CDER)
- Contact CDER

Office of Scientific Investigations

The goals of OSI are to:

- To verify the integrity of efficacy and safety data submitted to the FDA in support of new drug applications.
- To assure that the rights and welfare of human research subjects are protected.

OSI Accomplishes this by:

- Auditing and verifying clinical trial data submitted to the FDA in support of applications to demonstrate the safety and efficacy, or bioequivalence, of drugs for human use;
- Directing inspections of Institutional Review Boards (IRBs) for compliance with standards and regulations designed to protect the rights and welfare of human research subjects; and
- Ensuring that investigators, sponsors, and contract research organizations who conduct nonclinical and clinical studies on investigational new drugs comply with United States laws and regulations covering good clinical practice and good laboratory practice.

In the News

- OSI Metrics Overview (January 2015)
- OSI IRB Restrictions Imposed Letters (September 2013)
- FDA Launches Patient Network website (April 2013)
- FDA is accepting comments for the Draft Guidance on Providing Summary Level Clinical Site Data for CDER's Inspection Planning (December 2012)
- FDA releases a Draft Guidance on Providing Summary Level Clinical Site Data for CDER's Inspection Planning (PDF) (December 2012)
- FDA releases new version of the Electronic Source in Clinical Investigations Draft Guidance (November 2012)
- OSI Information Request Webinar (November 2012)

OSI Request

PART I Tabular Listings of Site Information

- Tabular data for all sites in the study (pdf)
- Protocols and Annotated CRFs for each study (pdf)

PART II Line Listing by Site

- Subject data listings organized by site for each study (pdf)

PART III Site-Level Data Set

- Voluntary site level summary data for site selection tool across all pivotal studies (xpt)

PART II - Line Listing by Site

This section would provide subject data listings organized by site for each pivotal study:

Listing Number	Listing Description
1	Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
2	Subject listing for treatment assignment (randomization)
3	Subject listing of drop-outs and subjects that discontinued with date and reason
4	Evaluable subjects/ non-evaluable subjects and reason not evaluable
5	By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
6	By subject listing, of AEs, SAEs, deaths and dates
7	By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
8	By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint
9	By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
10	By subject listing, of laboratory tests performed for safety monitoring

Case Study
- Inspection of Study Sites and Information Request

- The request was received from USFDA OSI, ~2 months after an sBLA submission
- We were informed that the FDA will conduct on-site inspections, And
- the following information would be needed:
  - Copy of the study protocol
  - By subject listing of the primary and secondary endpoint efficacy parameters or events
  - By subject listing of Vital signs and laboratory results performed for safety monitoring
  - By subject listing of concomitant medications (Prior, concomitant medications, including prohibited medications).
  - Only Serious Adverse Events (SAEs)
  - Discontinued subjects and reason for discontinuation.
  - Protocol deviations reported.

How OSI Request is Handled
- Clarify the requirements

- There're several follow up questions for the OSI request, some general and some specific to particular listings:
  - Which patient population should be displayed on each listing? All patients
  - What data source should be used? Raw vs. Analysis datasets? Analysis data
  - Which data cutoff should be used (most updated data or primary CSR snapshot)? Consistent with CSR datasets
  - Should we use visit window for efficacy listing? Use time window
  - How to provide the listings? CDs
- Listing-specific questions

How OSI Request is Handled
- Programming strategy: a) Naming convention

- **Re-use CSR listings programs** to create subject level data listings by site using the following naming convention for the output: Site<*numeric-portion-sideid*>_listing<*nn*>_<*listing-description*>.pdf

Listing Number	Listing Description	Example
01	enroll	Site1001_listing01_enroll.pdf
02	randomization	Site1001_listing02_randomization.pdf
03	discontinuation	Site1001_listing03_discontinuation.pdf
04	perprotocol	Site1001_listing04_perprotocol.pdf
05	eligibility	Site1001_listing05_eligibility.pdf
06	AE	Site1001_listing06_ae.pdf
07	deviations	Site1001_listing07_deviations.pdf
08	efficacy	Site1001_listing08_efficacy.pdf
09	CM	Site1001_listing09_cm.pdf
10	safety	Site1001_listing10_safety.pdf

How OSI Request is Handled
Programming strategy: a) Naming convention (cont.)

So the following listings are created based on the naming conventions:

- Copy of the study protocol Part I
- By subject listing of the primary and secondary endpoint efficacy parameters or events Site1001_listing06_efficacy
- By subject listing of Vital signs and laboratory results performed for safety monitoring Site1001_listing03_vs Site1001_listing05_lb
- By subject listing of concomitant medications (Prior, concomitant medications, including prohibited mec Site1001_listing04_cm
- Only Serious Adverse Events (SAEs) Site1001_listing02_sae
- Discontinued subjects and reason for c Site1001_listing01_discontinuation
- Protocol deviations reported.

How OSI Request is Handled
Programming strategy: b) Mock-ups

- Site1001_listing01_discontinuation

Listing 1 Subject Discontinuation and Reasons for Discontinuation: Site 1001

Protocol: XXXXX

Subject ID	Treatment	Last Dosing Date	Reason for Treatment Discontinuation	Date of Study Discontinuation	Reason for Study Discontinuation
1001	Treatment A			2014−09−28	WITHDRAWAL BY SUBJECT
1002	Treatment B			2014−07−12	WITHDRAWAL BY SUBJECT

How OSI Request is Handled
Programming strategy: b) Mock-ups (cont.)

- Site1001_listing02_sae

Listing 2 Serious Adverse Events: Site 1001

Protocol: XXXXX

Subject ID	Treatment	MedDRA Preferred Term	Start Date of Adverse Event	End Date of Adverse Event
1001	Treatment A	PNEUMONIA	2014−06−24	2014−07−08
1002	Treatment B	NEPHROPATHY	2014−05−29	

How OSI Request is Handled
Programming strategy: b) Mock-ups (cont.)

- Site1001_listing03_vs

Listing 3 Vital Signs: Site 1001

Protocol: XXXXX

Parameter = Diastolic Blood Pressure

Subject ID	Treatment	Planned Visit	Measurement Date	Value	Unit
1001	Treatment A	SCREENING	2013-06-17	65	mmHg
		BASELINE	2013-07-03	65	mmHg
		WEEK 1	2013-07-10	60	mmHg
		WEEK 2	2013-07-17	65	mmHg

How OSI Request is Handled
Programming strategy: b) Mock-ups (cont.)

- Site1001_listing04_cm

Listing 4 Concomitant Medications: Site 1001

Protocol: XXXXX

CSR Snapshot

Subject ID	Treatment	Start Date	Class	Preferred Term
1001	Treatment A	01MAR2009	ANALGESICS	PARACETAMOL
1002	Placebo	01DEC2010	COUGH PREPARATIONS	AMBROXOL

How OSI Request is Handled
Programming strategy: b) Mock-ups (cont.)

- Site1001_listing05_lb

Listing 5 Laboratory Data: Site 1001

Protocol: XXXXX

Reporting Period

Parameter = Albumin

Subject ID	Treatment	Planned Visit	Date/Time of Specimen Collection	Value	Unit
1001	Treatment A	SCREENING	2014-01-28T08:20	45	g/L
		BASELINE	2014-02-18T09:18	45	g/L
		WEEK 1	2014-02-25T09:35	44	g/L
		WEEK 2	2014-03-04T08:15	44	g/L

How OSI Request is Handled
Programming strategy: b) Mock-ups (cont.)

- Site1001_listing06_efficacy

Listing 6 Efficacy Parameters: Site 1001

Protocol: XXXXX

Reporting Period

Parameter = Albumin

Subject ID	Treatment	Analysis Visit	Analysis Visit Flag	Date/Time of Specimen Collection	Primary efficacy endpoint	Raw Parameters(unit)
1001	Treatment A	SCREENING		45		890.5
		BASELINE	Y	45	N	734.3
		WEEK 1	Y	44	N	528.5
		WEEK 2	Y			

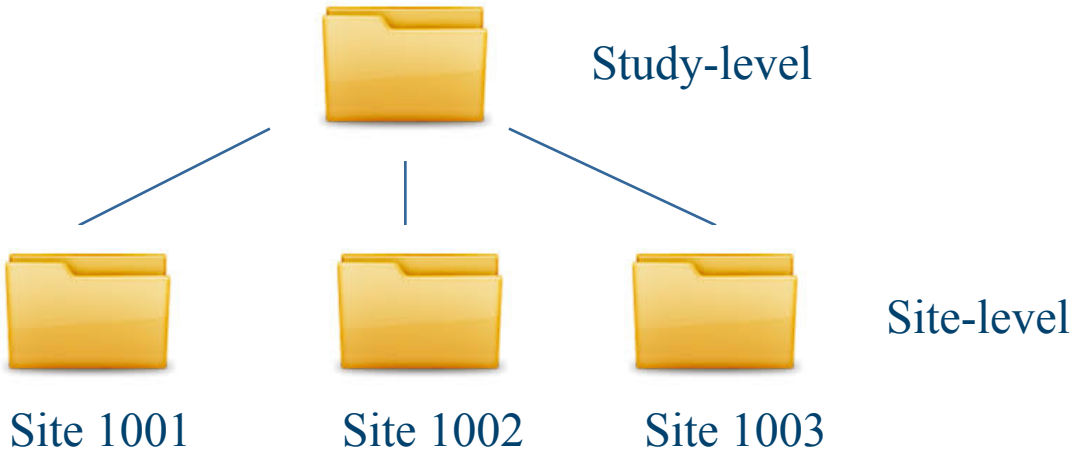
For derived or calculated endpoints, provide raw values used to generate the derived/calculated endpoint

How OSI Request is Handled
Programming strategy: c) Organize the outputs

- Run a program "**create_osi_folder.sas**" to organize the outputs in a more streamlined way

  The program is used to:

  - Create 1 study level folder
  - Create n site level folders where n is the number of sites in the study for which OSI listings have been produced
  - Copy the site level listings from the study area into these site level folders



Some Considerations

- More responsibility for programmers
- Cross-functional collaboration
- Reach out to FDA/OSI proactively for clarifications
- Take OSI listings into consideration when planning CSR listings, to enable reuse of outputs then to save resources

Final Remarks

- OSI package requirements for CDER's site inspection planning:
  - Part I Tabular Listings of Site Information
  - Part II Line Listing by Site
  - Part III Site-Level Data Set
- Experience of preparing OSI listings for an sBLA submission
  - Clarify the requirements
  - Programming strategy
- Some considerations

References

- **FDA OSI Website:** https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090085.htm
- **FDA OSI Slides:** Summary Level Information and Data for CDER s Inspection Planning
- **FDA Webinar:** Overview of Information Requested by CDER OSI for NDA and BLA Submissions

Q&A

Doing now what patients need next