Perspectives from CBER's Office of Compliance and Biologics Quality

Bioresearch Monitoring Experiences with Study Data Submissions to CBER

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Agenda

- FDA Data Standard Requirements
- CBER Bioresearch Monitoring Inspections
- Study Data Collection and Submission
- CBER Experiences with Submitted Data
- Suggestions for Sponsors
- FDA resources

FDA Study Data Standard Requirements-1

- Why should submitted study data be standardized?
  - Helps streamline FDA review process
  - Enables consistent use of analysis tools

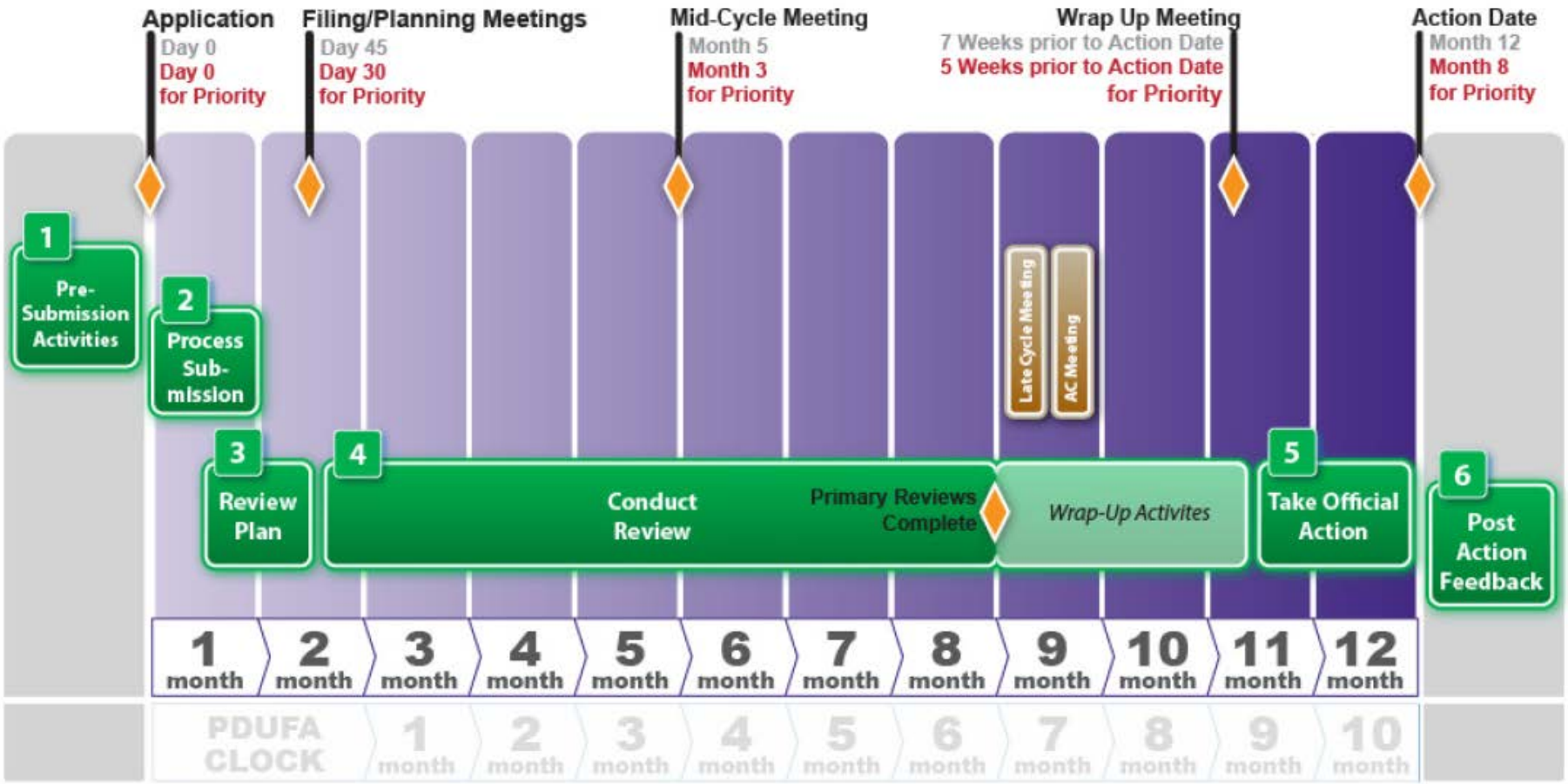
FDA Study Data Standard Requirements Resources Cited

- Guidance for Industry - Providing Regulatory Submissions in Electronic Format -Standardized Study Data
- CBER and CDER study data submissions link
- Factsheet-Study data standards

CBER Bioresearch Monitoring (BIMO) Branch

- Conduct pre-license and pre-approval data verification inspections
- Investigate complaints
- Answer questions about Good Clinical Practice (GCP)
- Help evaluate concerns about data integrity
  - Clinical investigators
  - Sponsor/Monitor/Contract Research Organizations /Sponsor Investigators
  - Institutional Review Boards
  - Good Laboratory Practice (GLP)/Nonclinical Lab

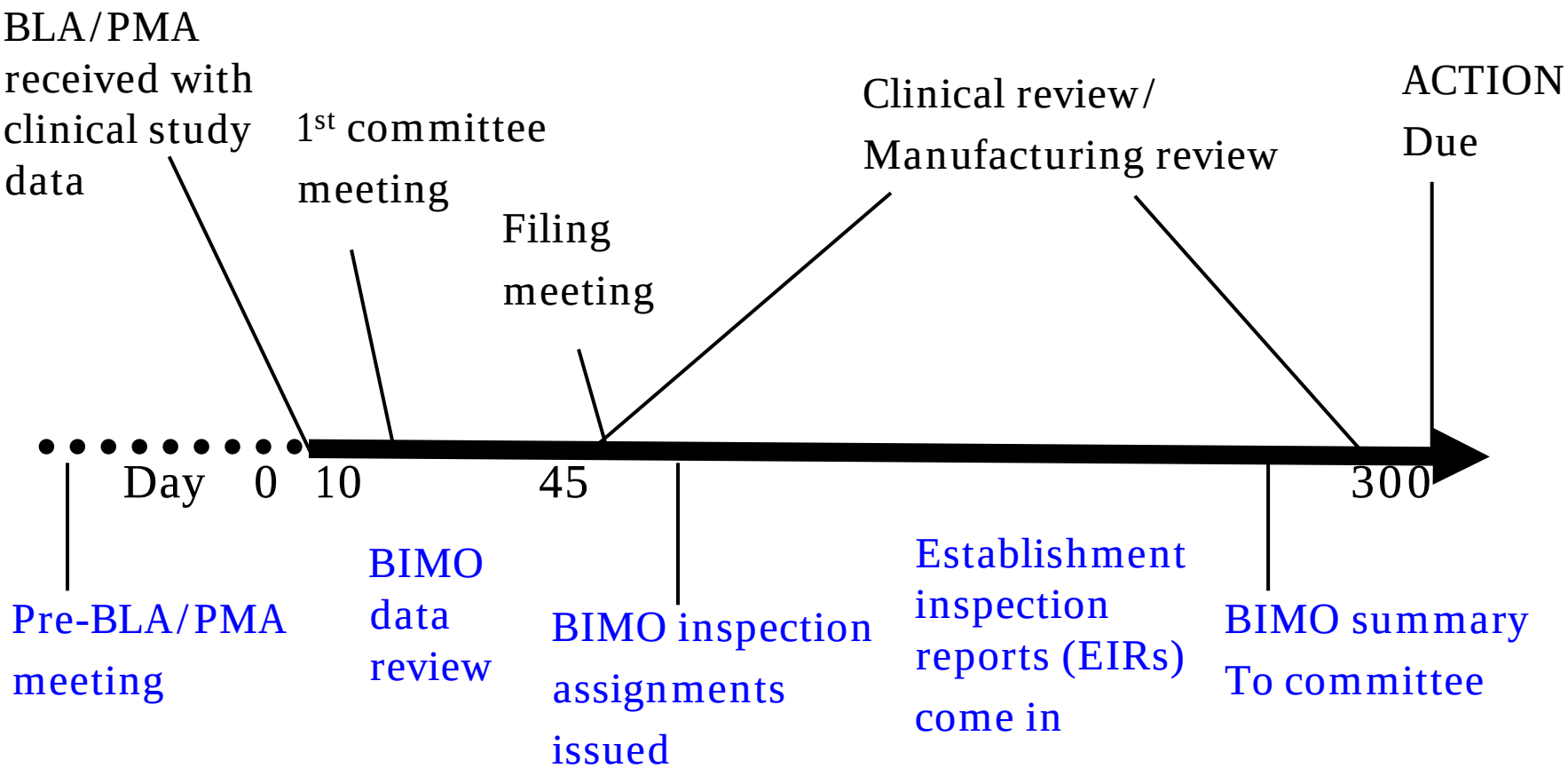
21st Century Review



From CDER's *21st Century Review Process Desk Reference Guide*

BLA Timeline-BIMO Review (10 month review period)

Priority (6 month) applications adjusted accordingly



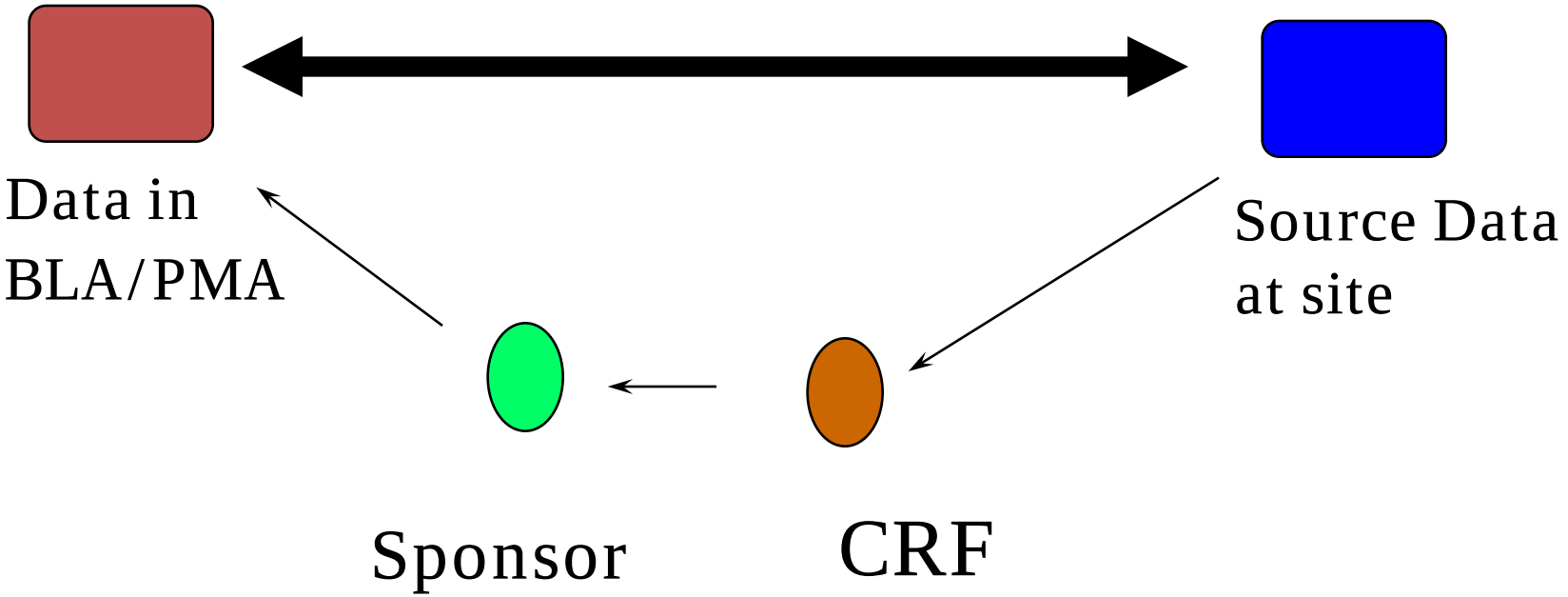
CBER BIMO site selection process for inspection-1

- BLA/sBLA/ANDA data tables
- Contents of the assignment-examples of data to be verified include
  - Adverse events
  - Protocol deviations
  - Subject eligibility
  - Blinding
  - Efficacy and Safety Endpoints

CBER BIMO site selection process for inspection-2

- Factors in site selection include, but not limited to
  - Subject distribution and disposition
  - Subject exclusions and discontinuation
  - Protocol deviations data
  - Inconsistent data for a site
    - Increased efficacy
    - Decreased incidence of adverse events
    - Randomization cannot be reconstructed
  - Inspection history of investigators
  - GCP problems reported by sponsor
  - Number of sub-investigators/satellite sites
  - Pending workloads in FDA geographic regions

Comparison of Data in BLA/PMA to Source During the Inspection



Challenges in data extraction from BLA data submissions for BIMO site selection

- SITEID variable was not included/available in all datasets except DM (Demography) dataset.
- Dataset submitted did not include standardized data variables. (see Slides 12 and 15)
- Protocol deviations submitted as pdf listings (see Slide 13)
- Subjects were not listed using standardized USUBJID variable. Instead subjects were listed under SUBJID/PID/PATIENT variable. (see Slide 14)
- Definition (Define) files were not user friendly and the definitions of dataset variables were not available. (see Slide 16)
- Critical endpoint data (rows of data) were missing. Possibly due to inadequate data validation by sponsor? (from previous talk)

More surprises if there were no Pre-BLA meetings!

CBER BIMO Experiences with Submitted Data-1

Data submitted as WELIM dataset instead of DV dataset for protocol deviations. Non-standardized variables were used.

	PID	CENTER	ELIM_V	ELIMCODE	ELI_TYPE
1	1	123	.		
2	2	123	1	111	AB
3	3	123	.		
4	4	123	.		
5	5	123	.		
6	6	456	.	112	AB
7	6	456	.	113	AB
8	6	456	.	114	AB
9	7	456	1	112	AB
10	8		1	112	AB
11	9	456	.	114	AB
12	10	456	.		

CBER BIMO Experiences with Submitted Data-2

Protocol deviations were submitted as pdf listings

Country	Site number	Issue category	Description of protocol deviation
Poland	111	Protocol deviation-Informed consent	On ICF there is incorrect date stated by parent, only year, no month and date for subject 12345
China	112	Protocol deviation-Other	In source documentation there is missing data on when the drug was returned, numbers of returned, DUNs and drug accountability (used / unused / lost vials).
United States	113	Protocol deviation-other	The normal ranges used in the local lab report did not consider the age difference. The ranges that were used in the report and transcribed into EDC reflect only the adult's range but not for the specific young age. It's the internal computer system issue of the study site because the normal range for different age group is actually available at the site, but just not on the lab reports.

The last row acknowledges potential issues in the integration of different computer systems used during data collection

CBER BIMO Experiences with Submitted Data-3

- Protocol deviation submitted in non-standard format and with <u>incomplete data</u>

STDYSITE	PATIENT	REASON 1	REASON 2
111	123456	Subject withdrawal, because it is unclear whether subject received the vaccine. Subject #123456 had the same randomization sticker on the source document. Undetermined which vaccine was received by wh	

- Incomplete information for a protocol deviation under REASON 1
- Instead of USUBJID the dataset included the variable PATIENT

CBER BIMO Experiences with Submitted Data-4

- Protocol deviations were submitted as "Comments" in COMMENTS (CO) dataset

RDOMAIN	USUBJID	COVAL
MB	100-5001-123456	No nasal culture swab received
QS	100-5001-123457	Based on the documentation provided, the subject can be considered immuno-competent.

- In another study-no corresponding definition submitted for a column variable in ADSL dataset-inadequate validation?

CBER BIMO Experiences with Submitted Data-5

Example of a Definition file that is not useful to the review:

[redacted]

Elements te.xpt Trial Inclusion/Exclusion Criteria ti.xpt Trial Summary ts.xpt Trial Visits tv.xpt Comments co.xpt Demogra
ds.xpt Protocol Deviations dv.xpt Healthcare Encounters ho.xpt Medical History mh.xpt CRS Events xc.xpt Drug Accountal
Results lbal.xpt Cytokine Laboratory Test Results lbcy.xpt B Cell Aplasia Results lbly.xpt Microbiology Specimen mb.xpt
Subject Status ss.xpt Tumor Results tr.xpt Tumor Identification tu.xpt Vital Signs vs.xpt Findings About Events or Intervent
suppdd.xpt Supplemental Qualifiers DM suppdm.xpt Supplemental Qualifiers DS suppds.xpt Supplemental Qualifiers DV s
suppho.xpt Supplemental Qualifiers IE suppie.xpt Supplemental Qualifiers IS suppis.xpt Supplemental Qualifiers LBAL sup
suppmi.xpt Supplemental Qualifiers MO suppmo.xpt Supplemental Qualifiers PC supppc.xpt Supplemental Qualifiers PR su
Supplemental Qualifiers TU supptu.xpt Supplemental Qualifiers CRS Events suppxc.xpt Study Identifier Domain Abbreviat
Identifier Domain Abbreviation Element Code Description of Element Rule for Start of Element Rule for End of Element Pl
Criteria Versions Study Identifier Domain Abbreviation Sequence Number Group ID Trial Summary Parameter Short Nam
Version of the Reference Terminology Study Identifier Domain Abbreviation Visit Number Visit Name Planned Study Day
Subject Identifier Sequence Number Identifying Variable Identifying Variable Value Comment Study Identifier Domain Ab
Treatment Date/Time of Last Study Treatment Date/Time of Informed Consent Date/Time of End of Participation Date/Tim
Code Description of Actual Arm Country Date/Time of Collection Study Day of Collection Study Identifier Domain Abbrev
Element Study Day of End of Element Planned Order of Element within Arm Description of Unplanned Element Study Iden
Start of Visit Study Day of End of Visit Description of Unplanned Visit Study Identifier Domain Abbreviation Unique Subj

CBER BIMO Experiences with Submitted Data-6

Examples of "Do's"

- A DV dataset and a good "definition" file

STUDYID	DOMAIN	USUBJID	DVDECOD	DVTERM	DVCAT
AB1-C11	DV	AB1-C11-101001	Informed Consent	Minor PD - Subject 101001 inadvertently dated the Data Privacy Consent Form with the incorrect year.	
AB1-C11	DV	AB1-C11-101001	Visit Schedule	Visit not performed as scheduled. Week 32 was not conducted within - 14 days of expected visit date.	
AB1-C11	DV	AB1-C11-101002	Visit Schedule	Visit not performed as scheduled. Week 28 was not conducted within - 14 days of expected visit date.	
AB1-C11	DV	AB1-C11-101002	Procedures/Tests	MINOR PD: Site shipped week 0 serum on 22May2016 and was logged out on shipping log. Sample was not receive	
AB1-C11	DV	AB1-C11-101002	Procedures/Tests	Minor PD: Site staff inadvertently did not capture subject 101002's temperature during their Screening Visit.	
AB1-C11	DV	AB1-C11-101002	Procedures/Tests	Partial Vital signs completed at visit Screening.	
AB1-C11	DV	AB1-C11-101003	Visit Schedule	Major PD- Subject 101003 had their Week 4 visit OOW.	
AB1-C11	DV	AB1-C11-101003	Visit Schedule	IP injection not administered as scheduled at visit Week 4.	Vaccine given outside protocol specified ...

DM (Demographics)

DM (Demographics) -- SPECIAL PURPOSE								dm.xpt
Name	Label	Key	Type	Length	Controlled Terms or Format	Origin	Role	Comment
STUDYID	Study Identifier	1	text	6	["AB1-C11"]	CRF Page 1	Identifier	AB1-C11
DOMAIN	Domain Abbreviation		text	2	["DM"]	Assigned	Identifier	
USUBJID	Unique Subject Identifier	2	text	15		Derived	Identifier	See Method (MT.CM.DM.USUBJID)
SUBJID	Subject Identifier for the Study		text	7		CRF Page 10	Topic	
RFSTDTC	Subject Reference Start Date/ Time		datetime		ISO 8601	CRF Page 12, 13, 14	Record Qualifier	
RFENDTC	Subject Reference End Date/Time		datetime		ISO 8601	CRF Page 42, 43, 44, 45	Record Qualifier	

Suggestions for Good Quality Data Submission

- Study specific data collection by sponsor
  - Sponsor develops protocol specific CRFs
- Advance discussions with CBER about esource data collection and/or data extraction from electronic data capture (EDC) systems and data integration
- Advance discussion of study data standardization plan (SDSP) including the domains and variables to be submitted early on during the study

Good quality data that comes through the FDA gateway could potentially avoid delay in our inspection site selection process

Information For Industry

Click for:

- CDER eData Team at: eDATA@fda.hhs.gov
- CBER CDISC Contact: CBER.CDISC@fda.hhs.gov
- Guidance for Industry: Computerized Systems Used in Clinical Investigations
- Guidance for Industry: Electronic Source data in Clinical Investigations
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data
- Study Data Technical Conformance Guide
- Technical Rejection Criteria for Study Data
- PDF of today's slides
- Email any remaining questions to us at: CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type in your questions now.

Click Here for Evaluation and Certificate

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