Perspectives from CBER’s Office of Compliance and Biologics Quality

Bioresearch Monitoring Experiences with Study Data Submissions to CBER

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Office of Compliance and Biologics Quality (OCBQ)
Division of Inspections and Surveillance
July 13, 2017
Agenda

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


CDER Small Business and Industry Assistance (SBIA) Webinar
July 13, 2017
BLA Timeline-BIMO Review
(10 month review period)

Priority (6 month) applications adjusted accordingly

- BLA/PMA received with clinical study data
- 1st committee meeting
- Filing meeting
- Clinical review/Manufacturing review
- BIMO inspection assignments issued
- Establishment inspection reports (EIRs) come in
- BIMO summary To committee

Pre-BLA/PMA meeting

Day 0 10 45 300

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CDER Small Business and Industry Assistance (SBIA) Webinar
July 13, 2017
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

Data in BLA/PMA

Sponsor

CRF

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

<table>
<thead>
<tr>
<th>PID</th>
<th>CENTER</th>
<th>ELIM_V</th>
<th>ELIMCODE</th>
<th>ELI_TYPE</th>
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<td>1</td>
<td>123</td>
<td></td>
<td></td>
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<td>2</td>
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CBER BIMO Experiences with Submitted Data-2

Protocol deviations were submitted as pdf listings

<table>
<thead>
<tr>
<th>Country</th>
<th>Site number</th>
<th>Issue category</th>
<th>Description of protocol deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland</td>
<td>111</td>
<td>Protocol deviation-Informed consent</td>
<td>On ICF there is incorrect date stated by parent, only year, no month and date for subject 12345</td>
</tr>
<tr>
<td>China</td>
<td>112</td>
<td>Protocol deviation-Other</td>
<td>In source documentation there is missing data on when the drug was returned, numbers of returned, DUNs and drug accountability (used / unused / lost vials).</td>
</tr>
<tr>
<td>United States</td>
<td>113</td>
<td>Protocol deviation-other</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 **incomplete** data

<table>
<thead>
<tr>
<th>STDYSITE</th>
<th>PATIENT</th>
<th>REASON 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>123456</td>
<td>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 whom</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Incomplete information for a protocol deviation under **REASON 1**
- Instead of USUBJID the dataset included the variable PATIENT
Protocol deviations were submitted as “Comments” in COMMENTS (CO) dataset

<table>
<thead>
<tr>
<th>RDOMAIN</th>
<th>USUBJID</th>
<th>COVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MB</td>
<td>100-5001-123456</td>
<td>No nasal culture swab received</td>
</tr>
<tr>
<td>QS</td>
<td>100-5001-123457</td>
<td>Based on the documentation provided, the subject can be</td>
</tr>
<tr>
<td></td>
<td></td>
<td>considered immuno-competent.</td>
</tr>
</tbody>
</table>

In another study—no corresponding definition submitted for a column variable in ADSL dataset—inadequate validation?
Example of a Definition file that is not useful to the review:
CBER BIMO Experiences with Submitted Data-6

Examples of “Do’s”
- A DV dataset and a good “definition” file
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.

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