BIMO: Requirements for Clinical Site Data and Subject Level Data Listings for FDA CDER's Inspection Process

Requirements for Clinical Site Data and Subject Level Data Listings for FDA CDER's Inspection Process (also called BIMO submission or OSI Pre-NDA request).

As part of the regulatory review process, the FDA conducts site inspections to ensure that clinical investigators, sponsors, and Institutional Review Boards (IRBs) comply with FDA regulations. The current submission format for study data in NDA and BLA packages does not facilitate efficient site selection for the FDA because these data are submitted as subject-level data. Therefore, the FDA has requested that pharmaceutical companies submit data that describes the characteristics and outcomes of clinical investigations at the site level. The FDA uses this data to plan their site inspections. The FDA refers to the request for site-level data as the OSI Pre-NDA request, where OSI is the FDA Office of Scientific Investigation. The submission of data for this request is also sometimes referred to a Bio-research Monitoring Program (BIMO) submission because the data is placed in the BIMO section of Module 5 in the eCTD. The FDA Bio-research Monitory Program (BIMO) develops guidelines for inspections of clinical investigators, sponsors, and Institutional Review Boards (IRBs). The FDA Office of Scientific Investigations (OSI) manages the BIMO program for drugs, and the FDA Office of Inspections and Surveillance manages the BIMO program for biologics.

There are three parts to the request to be provided to the FDA:

- 1 General study related information and specific Clinical Investigator information.
- 2 Subject-level data listings by site, for pivotal studies.
- 3 Site-level dataset in a standardised electronic format (Voluntary).

Submission teams will need to consult with their FDA review team during pre-NDA or pre-BLA communications to determine what Summary Level Clinical Site data to provide for their submission. For some submissions, submitting general study related information (Part 1) and subject-level data listings by site (Part II) may be sufficient. In other cases, the FDA may also request the site-level dataset (Part III). Per the FDA guidance document **Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning**, the site-level dataset 'should contain data from all major (e.g. pivotal) studies used to support safety and efficacy in the application, including studies with different treatment indications'. If a site-level dataset is needed, the FDA and sponsor will need to discuss and decide exactly what studies to include in the dataset and also agree on details about the content.

The site-level dataset to be provided to the FDA will come from several sources, such as clinical databases (SDTM and ADaM data), the Clinical Trial Management System (for investigator information), Financially systems (for info on financial payments to sites and investigators), and Regulatory (for NDA and BLA numbers). Consequently, the preparation of clinical site data is generally a cross-functional task involving groups such as Clinical Site Management, Regulatory, and Clinical Statistics and programming.

Depending on the specific requirements for a submission, the task of providing Summary level Clinical Site data to the FDA may require a lot of time and resources. Pre-planning is essential.

Details of OSI Request for Summary Level Clinical Site Data:

The FDA Office of Scientific Investigations (OSI) may request that sponsors provide the following information. Below is an example of the OSI Requests and may vary for your submission:

Office of Scientific Investigations (OSI) Requests

- *The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspections assignments, and the background packages that are sent with those assignments to the FDA field Investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.*
- *The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.*

I. Request for general study related information and specific Clinical Investigator Information (Note: If items are provided elsewhere in submission, describe location or provide link to requested information).

- 1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 2/3 clinical trials:
  - a) Site number
  - b) Principal investigator
  - c) Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e. phone, fax, email)
  - d) Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e. phone, fax, email)

- 2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 2/3 clinical trials:
  - a) Number of subjects screened for each site by site
  - b) Number of subjects randomised for each site by site
  - c) Number of subjects treated who prematurely discontinued for each site by site

- 3. Please include the following information in a tabular format in the NDA for each of the completed Phase 2/3 clinical trials:
  - a) Location of Trial Master File (actual physical site(s) where documents are maintained and would be available for inspection)
  - b) Name, address and contact information of all CROs used in the conduct of the clinical trials
  - c) The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
  - d) The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc)

- 4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

- 1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
  - a) Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b) Subject listing for treatment assignment (randomisation)
  - c) Subject listing of drop-outs and subjects that discontinued with date and reason
  - d) Evaluable subjects/non evaluable subjects and reason not evaluable
  - e) By subject listing of eligibility determination (clinical investigator assessment of each inclusion and exclusion criterion should be included)
  - f) Adverse event listings (inclusive of preferred/investigator terms, start/stop time and date, investigator assessment of relatedness to study drug, seriousness/severity, treatment for AE, action taken, and outcome):
    - i. By subject listing, of AEs, SAEs, deaths and dates
    - ii. By subject listing, of AEs of special interest (Hepatic events, Skin related events, Diarrhoea, Visual disorders, Cardiac related events, and Pneumonitis)
  - g) By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h) 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. For example, specific data points (e.g. target/non-target lesion MRI /CT measurements, development of new lesions, non-measurable disease burden assessment, if used, etc) used by the clinical investigator to make assessment of overall response for subjects should be included as well as the clinical investigator's overall assessment.
  - i) By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j) By subject listing, of testing (e.g. ECG, laboratory) performed for safety monitoring

Note: All listings are by site and subject.

- 2. FDA requests that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:

III. Request for Site-Level Dataset in Standardised Electronic Format (VOLUNTARY)

- a) The summary-level clinical site dataset is a single dataset containing data from all the major studies in the submission, including studies with different treatment indications. the dataset should not contain data from biopharmaceutical, clinical pharmacology, or animal studies
- b) The dataset should contain one record per study, clinical site, and treatment arm, and primary endpoint, for the intent-to-treat (ITT) population. Clinical sites included in multiple studies will have separate records for each study
- c) The summary level clinical site dataset should be provided in XPT format, it should be named 'clinsite.xpt' and it should comply with the format described in the FDA document 'Specification for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning'

Submitting Site-Level Data in eCTD Format to the FDA

A. Data submitted for OSI review belongs in Module 5 of the eCTD

- Note that item I is the general study related information and specific Clinical Investigator information, item II is the subject level data listings by site, and item III is the site level dataset
- For itms I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf title for this data should be named 'BIMO (list study ID, followed by brief description of file being submitted). In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this SFT should be 'bimo'. Files for items I, II and II below should be linked into the BIMO STF, using file tags indicated below. The item III site-level dataset filename should be 'clinsite.xpt'.

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide in included, it should be included in the BIMO Study Tagging File (STF). The leaf title should be 'BIMO Reviewer Guide'. The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

- FDA's Draft Guidance for Industry: Providing Submissions in Electronic Format - Summary Level Clinical Site Data for CDER's Inspection Planning
- FDA's Summary level Clinical Site Data Specifications: 'Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning
- FDA Bioresearch Monitoring Program (BIMO)
- PHUSE Project Standardizing Data within the Inspection Site Selection Process
- PHUSE presentation on BIMO (OSI) Deliverables for FDA NDA Filing (provides general overview)
- PHUSE 2014 paper on Submitting Summary Level Site Data: Overview, Implementation, and Case *Studies. This paper provides advice on pre-planning and points to consider