Paper SA05

FDA Dataset Walkthrough – Statistical Programmer Perspective

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ABSTRACT

FDA dataset walkthroughs are a complement to application orientation meetings and enable sponsor organizations to provide detailed eCTD overview and salient features of the submission data package to the FDA review team early in the review cycle. We share statistical programming perspectives from face to face as well as virtual dataset walkthrough meetings conducted for recent (s)NDA and (s)BLA filings to the FDA.

Key areas of focus include; a) Overview of datasets and variables that support key analyses to assess the overall benefit risk profile of the product; b) Identification of critical tabulations and analysis datasets within specific modules of the eCTD that contain data that is the subject of prior discussions and interactions with the agency; c) Navigation through the eCTD with emphasis on identification of key analyses populations and analysis rules; d) Strategies to prepare for review team questions during open discussion following the sponsor presentation.

INTRODUCTION

After receipt of a new drug application, biologics license application, or supplement for a new indication, the Food and Drug Administration (FDA) can conduct Application Orientation Meeting (AOM) and Dataset/Technical Walkthrough Meetings as part of their review in assessing safety and efficacy of drugs.

AOMs require sponsors to deliver a formal presentation that summarizes findings from their development program that support the marketing application. The FDA typically requests an AOM to directly discuss the content or format of the company's application and to gain important insights early in the regulatory process.

We outline here some statistical programming perspectives from recent request for AOMs and Technical dataset walkthroughs with a particular focus on the dataset walkthrough. These requests are primarily for orphan indications and breakthrough therapies. However, the agency may also request an AOM for non-priority applications that pose unique regulatory policy questions, and we include some experiences from such submissions as well.

BACKGROUND AND PURPOSE OF MEETING

AOM meetings are an opportunity for the sponsor to walk through the submission with the FDA review team and to provide their perspective. For the FDA it is an early opportunity to hear the sponsor's point of view and to ask any questions they may already have in their review of the submission.

AOMs are typically two-part meetings with each part having 35 to 40 minutes allotted for a sponsor presentation and 25 to 20 minutes for a question-and-answer period immediately following, where there is an opportunity for the FDA reviewers and other FDA attendees to ask questions. The first part is a one-hour application orientation meeting, the second part includes a one-hour technical dataset walkthrough, where the applicant may review the submission datasets with the FDA review team.

MEETING ATTENDEES

Dataset walkthrough meeting attendees include, but are not limited to, the following attendees from the sponsor and FDA.

Sponsor Team:

- Clinical leader and other clinical team members
- Regulatory team
- Statistical leaders and study statisticians
- Statistical programming leader and programmers
- Clinical pharmacology team members
- Global medical safety team members

FDA Team:

- FDA Clinical Reviewers
- FDA Statistical reviewers
- FDA Clinical Pharmacology reviewers

MEETING AGENDA

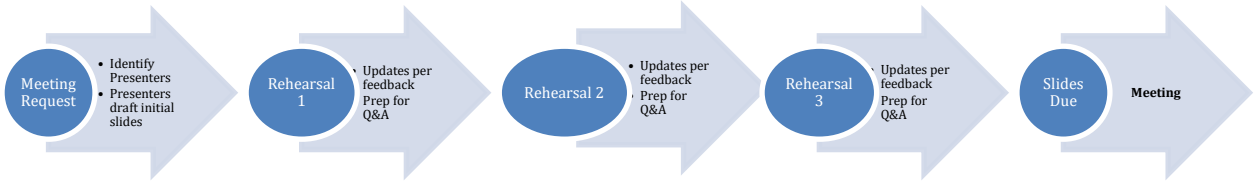
The Dataset walkthrough meetings start with a presentation on the background of the submission and specific data topics which could be review issue or topics requested by FDA in type B meeting. The location of datasets and associated files in the eCTD are then covered via presentation slides as well as a eCTD demonstration. Following that there is a questions and discussions session.

PREPARATION FOR DATASET WALKTHROUGH MEETING

To ensure a successful walkthrough meeting, it is important for the sponsor to carefully prepare for the meeting. This preparation should include, reviewing data for accuracy and completeness, preparing slides or other visual aid/live demo to help present the data in an easy-to-understand manner, and preparing a list of questions or concerns that the sponsor would like to discuss with the FDA reviewer during the meeting. It is also important to assemble a team of individuals who have expertise in the data and are familiar with the product.

As prework prior to the meeting, Regulatory affairs creates draft slides and identifies presenters. Biostatistics, Programming and Clinical pharmacology teams update their sections based on what team wants to present in terms of content. After slides are prepared, the regulatory team plans for rehearsal meeting/s where all the presenters present their slides to the team.

For an AOM in the virtual setting, there is usually a technical check an hour before with the FDA regulatory project manager, to confirm who from the sponsor will share slides and to perform an audio check for presenters. Presenter's login 5-10 mins before the meeting start time so that they can test connection.



SPONSOR STATISTICAL PROGRAMMING EXPERIENCE

Recent dataset walkthrough meeting experiences reveal a few areas commonly covered in sponsor presentations and Q&A session. Statistical programming perspectives on these are outlined here at a high level and a particular area is elaborated further in Example I: eCTD overview.

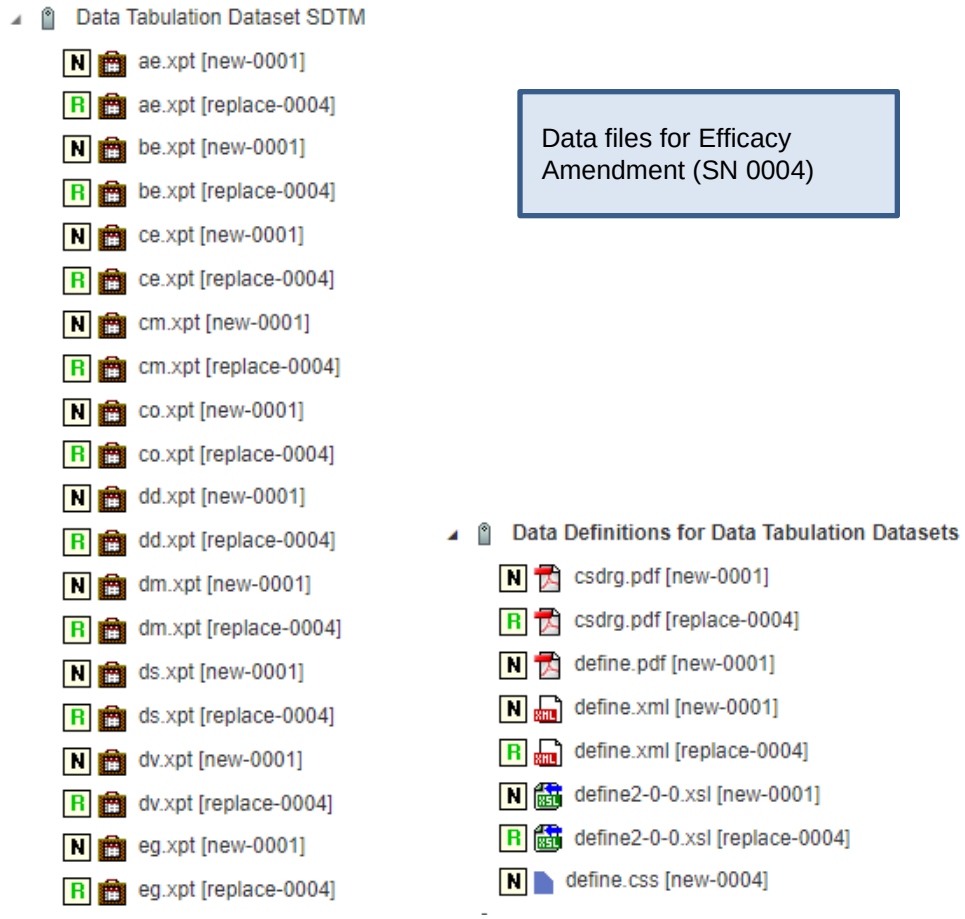
- Identification of derived variables or flags for key populations of interest - Rather than regularly provided flags for ITT or safety the focus here is on identifying subjects in registrational cohorts, subjects treated at recommended phase 2 dose or subjects meeting a specific pre-treatment or baseline disease criteria.
- Identification of parameters for investigator assessed responses and those assessed by independent review - Additionally, team should be prepared to discuss intermediate datasets available for quantitative evaluation of imaging / lab data that are utilized in determination of overall response.
- Overview of submission datasets in eCTD for multiple data releases or resubmission of datasets - For Real Time Oncology Review (RTOR) submission sponsors should include a presentation on updated datasets sent after early submission package. When updated efficacy data based on longer follow-up is included as part of the initial filing to supplement the primary analysis, sponsors should plan to include this in their presentation and for potential Q&A. Details of data presented in such a scenario are outlined in Example I: eCTD overview

In addition there are novel aspects of a submission that are of interest to the review team. These should be covered in sponsor presentations and are likely to be a part of the Q&A. One example is datasets related to Cytokine Release Syndrome (CRS) and Neurotoxicity (NT) events for CAR-T cell therapy and bispecific antibodies. Details of such an agency request from a Type B meeting, and the dataset overview provided at a dataset walkthrough meeting are included in Example II: Type B meeting request dataset overview. Other novel dataset examples are supportive real world data or external control arm data submitted as part of the filing.

EXAMPLE I: ECTD OVERVIEW

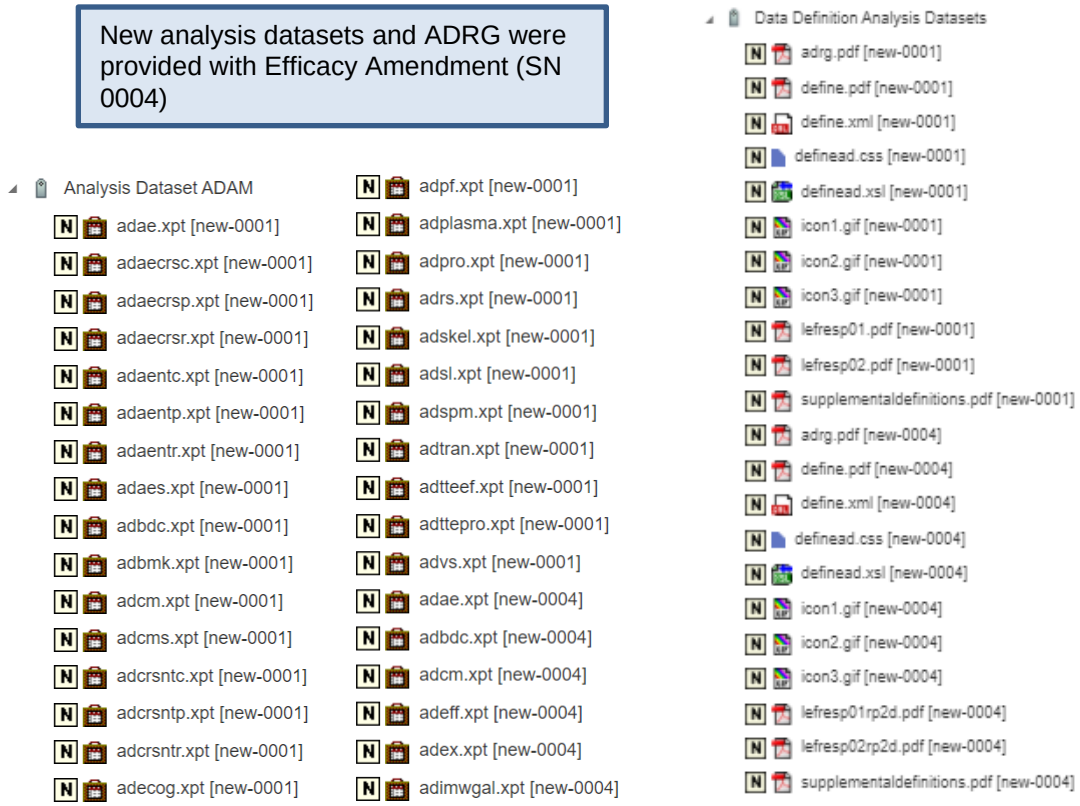
eCTD Screenshots below provide overview of the datasets and supportive documentation for an efficacy update provided along with the primary analysis CSR as part of a BLA filing. The screen shots show how sequence numbers for the submitted datasets can enable identification of those provided in support or primary analysis CSR vs those for the efficacy update.

Module 5.3.5.2: Data Tabulation Datasets and Definitions



Module 5.3.5.2: Analysis Datasets and Data Definition files

New analysis datasets and ADRG were provided with Efficacy Amendment (SN 0004)



EXAMPLE II: TYPE B MEETING REQUEST DATASET OVERVIEW

Review of Cytokine Release Syndrome (CRS) and Neurotoxicity (NT) adverse events is a critical area of focus for CAR-T cell therapies and bi-specific antibodies. Comprehensive overview of adverse event attributes, therapeutic interventions and grading criteria utilized are requested during pre-submission regulatory interactions. We outline here, key information presented at dataset walkthrough meetings on this topic.

The request was for separate datasets for CRS and NT with subject and event level information

CRS Dataset:	NT Dataset:
• Each row assigned to a unique subject with CRS diagnosis per investigator's assessment. • Key elements of CRS: fever, hypotension, hypoxia. • CRS treatment: oxygen, vasopressors, tocilizumab, corticosteroids, ventilator support, ICU stay, other interventions (e.g., other IL-6 inhibitors), if used. • Details of treatment: For example, number of vasopressors and type of oxygen delivery (e.g., low-flow nasal cannula, facemask, etc.), need to be captured to grade CRS accurately by the proposed ASTCT (American Society for Transplantation and Cellular Therapy) grading criteria. Other treatment details should also be provided – for example, dose of steroids and start/stop dates for each intervention. • Date and day of study treatment and start and end dates and study days for CRS to capture timing of CRS onset and duration. • Maximum CRS grade based on ASTCT consensus grading system • Organ dysfunction (SOC and PT) grade based on CTCAE version 5.0 seen in association with CRS. • CRS grading by Lee criteria to enable comparison of toxicity profile across products. • Flag for subjects in CRS dataset that develop neurotoxicity concurrently with CRS, with maximum grade.	• Each row assigned to a unique subject. • NT timing in relation to study treatment and in relation to CRS (e.g. preceding CRS, occurring concurrently with CRS, following CRS, or an isolated event). • Date and day of study treatment and start and end dates and study days for NT to capture timing of NT onset and duration. • Therapeutic intervention with details/outcome. • Outcome: e.g., resolution, worsening, unchanged but ongoing. • Maximum grade of NT based on ICANS (immune effector cell-associated neurotoxicity syndrome) ASTCT consensus grading system • NT symptoms/signs not included under ICANS, such as tremor and dysarthria should be graded with CTCAE version 5.0. • Both Neurologic and Psychiatric SOC adverse events should be captured in the NT dataset

To address this request, subject and event level datasets were created for CRS and NT events as well as specific variables added to the ADAE dataset. The define and ADRG provided details on the datasets and variables and an overview of these datasets were also provided during the dataset walkthrough as included below.
Note that we do not suggest this as an analysis dataset standard for such requests rather use this as an example of datasets supporting critical but non-standard analysis requests that can be presented at a dataset walkthrough.

ADAE – Select key components related to CRS/NT

- **AE of Special Interest variable, AESCAT:**
  - AESCAT = CRS, SYMPTOM OF CRS
  - AESCAT = ICANS, SYMPTOM OF ICANS
- **Variables identifying CRS/NT records:**

CRS

- CRSFL CRS (Y/N)
- CRSSYMFL Symptom of CRS (Y/N)
- CRSTOX CRS grade by Lee for Phase 1
- ASTCTCRS CRS grade by ASTCT for Phase 2
- LCRSMAX Derived Max CRS grade by Lee criteria
- ASTCRSD Derived CRS ASTCT grade

NT

- NEUROFL Neurologic AE (Y/N)
- NEUTOXFL Neurotoxicity AE (Y/N)
- ASTCTICA ICANS grade by ASTCT for Phase 2
- ICNSYMFL Symptom of ICANS
- NTICANFL/NICANTOX Phase 1 AE assessed as ICANS (Y/N) / derived grade by ASTCT
- GRPAPHFL/GRPDELFL/GRPENCFL/GRPTRMFL PT grouping of aphasia / delirium / encephalopathy / tremor
- CRSCONFL ICANS concurrent with CRS

ADAECRS- Select key components of CRS event level dataset

CRS Dataset:

- Each row assigned to a unique subject with CRS diagnosis per investigator's assessment.
- Key elements of CRS: fever, hypotension, hypoxia.
- CRS treatment: oxygen, vasopressors, tocilizumab, corticosteroids, ventilator support, ICU stay, other interventions (e.g., other IL-6 inhibitors), if used.
- Details of treatment: For example, number of vasopressors and type of oxygen delivery (e.g., low-flow nasal cannula, facemask, etc.), need to be captured to grade CRS accurately by the proposed ASTCT (American Society for Transplantation and Cellular Therapy) grading criteria. Other treatment details should also be provided – for example, dose of steroids and start/stop dates for each intervention.
- Date and day of study treatment and start and end dates and study days for CRS to capture timing of CRS onset and duration.
- Maximum CRS grade based on ASTCT consensus grading system
- Organ dysfunction (SOC and PT) grade based on CTCAE version 5.0 seen in association with CRS.
- CRS grading by Lee criteria to enable comparison of toxicity profile across products.
- Flag for subjects in CRS dataset that develop neurotoxicity concurrently with CRS, with maximum grade.

Select key components/variables:

- AVISIT last treatment visit on or prior to the day in which the CRS occurred
- AETRTSDY date/time (study day) of last study agent dose on or prior to the CRS event
- AELNKID ID for any CRS events which are linked
- CRSSDTY/CRSEDTY start/end date (study day) of PT=CRS
- ASTCTCRS toxicity grade based on ASTCT
- CRSTOX toxicity grade based on Lee criteria
- CRSELE key elements of CRS in concatenation
- CRSORGD1-2 organ dysfunction (SOC/PT/max grade)
- CRSRELNT concurrent with neurotoxicity ([Y/N]/PT/Max Grade)
- CMSVASFL/CMMVASFL single/multiple vasopressor (Y/N)
- CRSOXYG type of supplemental oxygen
- CRSSTER steroids dose
- TOCITRT1 tocilizumab (start/stop/dose/frequency/route)
- CRSTRT01-4 other treatment for CRS (start/stop/dose/frequency/route)
- CRSICU ICU stay (admission/discharge date)

ADAENT – Select key components of Neurotoxicity event level dataset

NT Dataset:

- Each row assigned to a unique subject.
- NT timing in relation to study treatment and in relation to CRS (e.g. preceding CRS, occurring concurrently with CRS, following CRS, or an isolated event).
- Date and day of study treatment and start and end dates and study days for NT to capture timing of NT onset and duration.
- Therapeutic intervention with details/outcome.
- Outcome: e.g., resolution, worsening, unchanged but ongoing.
- Maximum grade of NT based on ICANS (immune effector cell-associated neurotoxicity syndrome) ASTCT consensus grading system
- NT symptoms/signs not included under ICANS, such as tremor and dysarthria should be graded with CTCAE version 5.0.
- Both Neurologic and Psychiatric SOC adverse events should be captured in the NT dataset

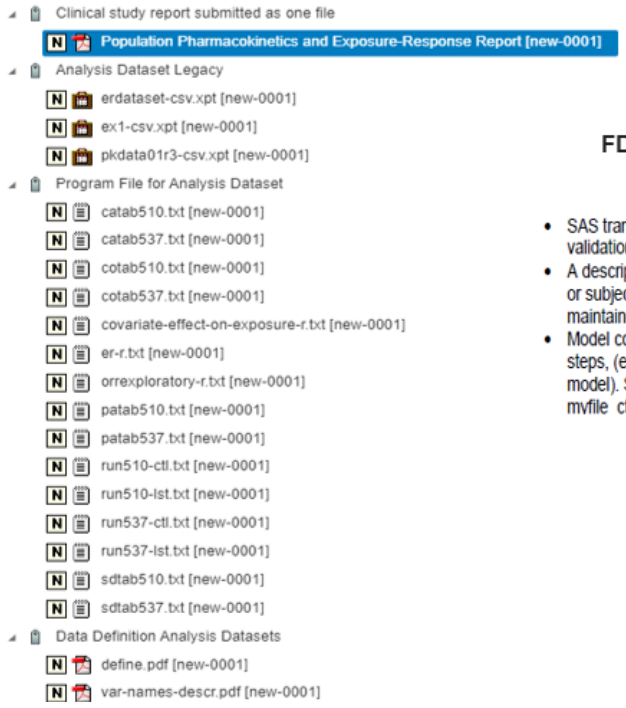
Select key components/variables:

- AVISIT last treatment visit on or prior to the day in which the CRS occurred
- AETRTSDY date/time (study day) of last study agent dose on or prior to the AE
- AELNKID ID for any AEs which are linked
- AETERM/AEDECOD/AESOC reported term/PT/SOC
- FDAGRP PT grouping
- NEUROFL neurologic AE (Y/N)
- NEUTOXFL neurotoxicity AE (Y/N)
- ICANSFL ICANS AE (Y/N)
- AESTDY/AEENDY start/end date (study day) of AE
- AEOUT outcome of AE
- TOXGRN toxicity grade based on CTCAE except for ICANS which is based on ASTCT
- NTXTRT1-5 treatment (start/stop/dose/frequency/route)
- NTXRELAE relative to CRS

EXAMPLE III: TYPE B MEETING REQUEST PK DATA OVERVIEW

eCTD Screenshot below outlines the information provided in response to an agency clinical pharmacology request at Type B meeting that was part of a dataset walkthrough presentation

Module 5.3.3.5: Population PK and Exposure-Response



FDA request (Type B meeting)

- SAS transport files (*.xpt) for all datasets used for model development and validation
- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- Model codes or control streams and output listings for all major model building steps, (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension (e.g., mvfile_ctl.txt, mvfile_out.txt)

RECOMMENDATIONS

In summarizing our experiences, we would like to provide the following recommendations to statistical programming teams who may be preparing to participate in an application orientation meeting and dataset walkthrough

- As part of the sponsor presentation, include screenshots of relevant datasets and supporting documentation from Modules 1-5 of eCTD. Module 5 screenshots should focus on CSR ADaM datasets, ADRG and Define.xml as well as BIMO deliverables and NCA / NonMEM analysis supporting the population PK and exposure-response analysis.
- Include in sponsor presentation as well as prepare to discuss during Q&A session, information about specific datasets and information requests the team may have received before the submission either in pre-NDA/BLA meetings or via questions during the review process.
- In virtual settings, co-ordinate with the regulatory affairs team to create a separate chat session, that enables contemporaneous discussion among sponsor extended team members to discuss and prepare responses to questions.
- Programming team representative should prepare for a live demonstration of eCTD once the presentation is complete.

- When addressing questions about specific datasets and variables, it is advisable to refer information already submitted as part of define or ADRG vs trying to open specific xpt datasets from eCTD.
- Have clinical team available to address questions on study design and conduct at dataset walkthrough.

CONCLUSION

The dataset walkthrough enables sponsor organizations to provide detailed eCTD overview and salient features of the submission data package to the FDA review team early in the review cycle. Questions and data requests arising from the pre-submission correspondence between the sponsor and the review team significantly shape the documents and datasets included in a submission. The dataset walkthrough provides the sponsor an opportunity to convey to the review team, details on specific datasets and variables that provide the information requested, facilitating greater efficiency in the review. It also provides an opportunity for a dialogue on the more technical data topics that may not be adequately focused on in other planned sponsor–agency interactions. A well planned and successful dataset walkthrough following an application orientation meeting can provide a positive experience for the sponsor and review team for the remainder of the review process.

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