

FDA Dataset Walkthrough – Statistical Programmer Perspective

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Opinions expressed are those of the presenters individually and are not the opinion or position of Janssen, Johnson and Johnson or its affiliates.

Agenda

1 Background of AOM and Dataset Walkthrough

2 Meeting Logistics

3 Preparing for the Dataset Walkthrough

4 Statistical Programming Experience

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Background of AOM and Dataset Walkthrough

Skin cells at 20x magnification

Background of AOM and Dataset Walkthrough

- 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. These meetings are an opportunity for the sponsor to walk through the submission with the FDA review team and to provide their perspective.
- 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. 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.
- 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

Meeting Logistics

Skin cells at 20x magnification

Meeting Agenda



Part 1 – Application Orientation Meeting

35 - 40 minutes Sponsor presentation
25 - 20 minutes Q&A and discussion



Part 2 – Dataset Walkthrough

35 - 40 minutes Sponsor presentation
25 - 20 minutes Q&A and discussion



The Dataset walkthrough presentation provides;
Background of the submission
Data topics which could be review issue or topics requested by FDA in type B meeting
Location of datasets and associated files in the eCTD and live demonstration of the same



Q&A period provides opportunity for the FDA reviewers and other FDA attendees to ask questions.

Meeting Attendees

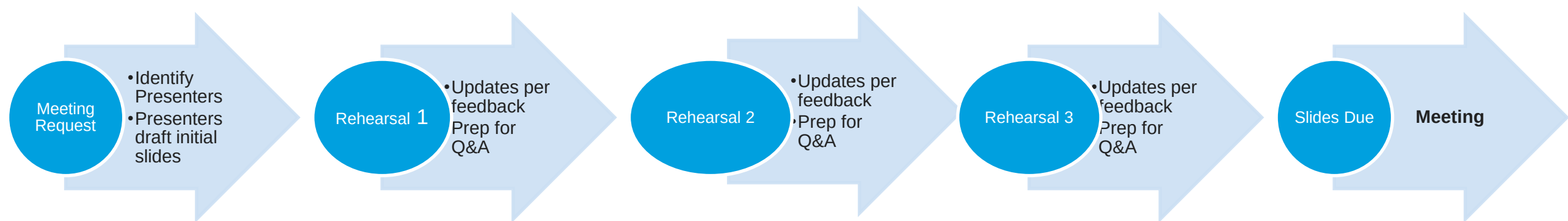
- Dataset walkthrough meeting attendees include, but are not limited to, the following attendees from the sponsor and FDA
 - Sponsor representatives:
 - Clinical leader and other clinical team members
 - Regulatory team
 - Statistical leaders and study statisticians
 - Statistical programming leader and programmers
 - Clinical pharmacology team members
 - Global medical safety team members
 - FDA representatives:
 - FDA Clinical Reviewers
 - FDA Statistical reviewers
 - FDA Clinical Pharmacology reviewers

Preparing for Dataset Walkthrough

Skin cells at 20x magnification

Preparing for Dataset Walkthrough

- To ensure a successful walkthrough meeting 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
 - Preparing a list of questions or concerns that the sponsor would like to discuss with the FDA reviewers during the meeting
 - Assembling 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 information team wants to present
 - Team conducts rehearsal meetings where all the presenters present their slides



Statistical Programming Experience

Skin cells at 20x magnification

Common Discussion Topics

- Identification of derived variables or flags for key populations of interest
 - Subjects in registrational cohorts,
 - Subjects treated at recommended phase 2 dose
 - Subjects meeting a specific pre-treatment or baseline disease criteria
- Response assessment for Oncology trials
 - Identification of parameters for investigator assessed responses and those assessed by independent review
 - 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
 - Updated datasets sent after early submission package For Real Time Oncology Review (RTOR)
 - Updated efficacy data based on longer follow-up included as part of the initial filing along with the primary analysis

Novel Discussion Topics

- Novel aspects of a submission that are of interest to the review team
- Datasets related to Cytokine Release Syndrome (CRS) and Neurotoxicity (NT) events for CAR-T cell therapy and bispecific antibodies
 - Real world data or external control arm data submitted as part of the filing
 - Population PK and exposure-response analysis as discussed in pre-submission correspondence

Example I : eCTD Overview

Module 5.3.5.2: Data Tabulation Datasets and Definitions

eCTD Screenshots show overview of the datasets and supportive documentation for an efficacy update provided along with the primary analysis CSR as part of a BLA filing.

Sequence numbers for the submitted datasets are highlighted to enable identification of those provided in support or primary analysis CSR vs those for the efficacy update.

Data Tabulation Dataset SDTM

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Data files for Efficacy Amendment (SN 0004)

Data Definitions for Data Tabulation Datasets

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N	define.css [new-0004]

Example I : eCTD Overview

Module 5.3.5.2: Analysis Datasets and Data Definition files

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

Analysis Dataset ADAM

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adaecrsc.xpt [new-0001]
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adrg.pdf [new-0004]
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icon2.gif [new-0004]
icon3.gif [new-0004]
lefresp01rp2d.pdf [new-0004]
lefresp02rp2d.pdf [new-0004]
supplementaldefinitions.pdf [new-0004]

Example II : CRS and NT 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.

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.	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
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Example II : CRS and NT dataset Overview

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 was provided during the 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

Example II : CRS and NT dataset Overview

ADAE CRS- 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
- AETRSDY 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)
- CRSTR01-4 other treatment for CRS (start/stop/dose/frequency/route)
- CRSICU ICU stay (admission/discharge date)

Example II : CRS and NT dataset Overview

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)
- NTXRELA relative to CRS

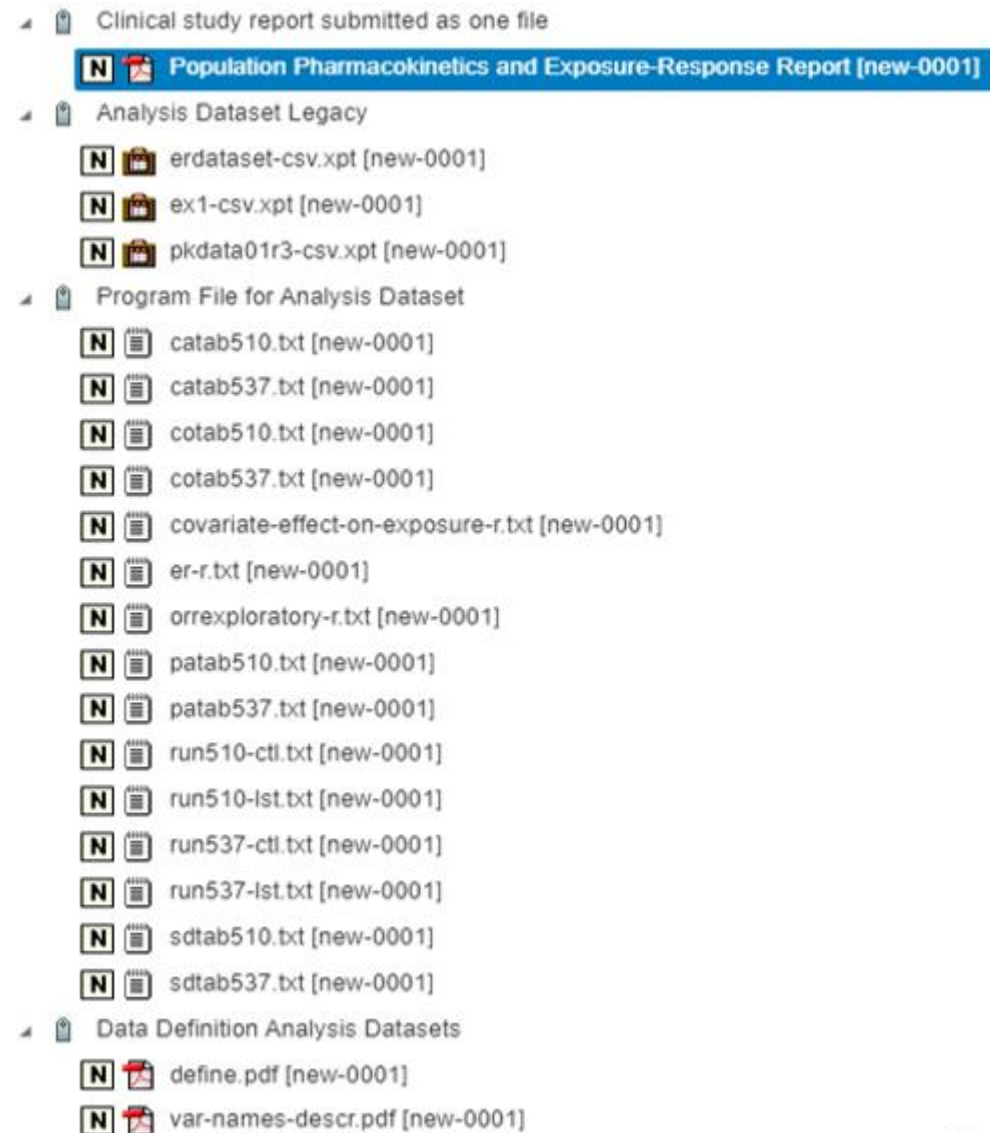
Example III : Pop PK and Exposure Response

Module 5.3.3.5: Population PK and Exposure-Response

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

Type B meeting request

- 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., myfile_ctl.txt, myfile_out.txt)



Recommendations

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Recommendations

Provide screenshots of relevant datasets and supporting documentation from Modules 1-5 of eCTD during sponsor presentation. Module 5 screenshots should focus on ADaM datasets, ADRG and Define.xml as well as BIMO deliverables and analysis supporting the population PK and exposure-response analysis.

Present 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 ready to address questions on study design and conduct at dataset walkthrough.

Summary



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 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.

Thank You

We would like to acknowledge the colleagues at Janssen who supported the dataset walkthroughs that were referenced in this presentation. Specifically, we would like to thank; Nicole Thorne, Eric Gibbs, Peter Hao Hu, Baoqing Li and Ronan Knab.

Questions



We welcome your comments and questions.
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