

Study Data Topics at FDA/CDER

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent the views or policies of the U.S. Food and Drug Administration

Outline

- Data-related review issues
- Importance of data standards
 - SDTM
 - ADaM



Data-related Review Issues

Data-related Review Issues

- Quality of SDRG, ADRG and define files
 - Insufficient information to understand and navigate tabulation and analysis datasets
 - Insufficient details to allow reviewers to understand the meaning, source, and derivation of each variable used in safety and efficacy analyses

Data-related Review Issues

- Statistical programs
 - Insufficient information/comments to understand and navigate programs
 - Macros used for analyses are called in programs, but not included in submission
- Missing versions of SAPs, protocols

Data-related Review Issues

- Datasets
 - Lack of appropriate patient identifier
 - Lack of analysis population flags
 - Lack of treatment phase variables
 - Lack of important baseline disease characteristic variables
 - Lack of important variables in efficacy or safety datasets

Data-related Review Issues

- Datasets (cont.)
 - Missing values
 - Identification of values that are truly missing vs. systematic missing
 - Records with imputed values not identifiable
- Other examples

Prevention of Data-related Review Issues

- For NDA, BLA, and ANDA studies that started after **December 17, 2016**, submit datasets using CDISC standards. Otherwise, follow CDISC standards as closely as possible
- Submit properly documented SDRG and ADRG

Prevention of Data-related Review Issues

- Provide statistical programs used to
 - Derive analysis datasets from tabulation datasets
 - Generate tables and figures associated with primary and secondary efficacy analyses
 - Generate additional information included in Section 14 Clinical Studies of the Prescribing Information (if applicable)
- Provide define files with adequate comments, bookmarks, and hyperlinks



Importance of Data Standards

Importance of Data Standards

- Data standards applied to submitted datasets are essential for the regulatory review of a drug submission
- Datasets are used by cross-disciplinary team members (i.e., clinical, statistical, clinical pharmacology, etc.)



Importance of Data Standards: An Example (SDTM)

Logically Skipped Items

- Patient-reported outcomes (PROs), a type of COA (clinical outcome assessment), are a key part of patient-focused drug development (PFDD)
- An increasing number of drug submissions have used PROs for efficacy in their primary and secondary endpoints

Logically Skipped Items

- A PRO instrument may have logically skipped items
- This occurs when an instrument item is asked conditionally, based on the response for a previous item in the instrument

Logically Skipped Items

1. Are you currently employed (working for pay)? NO YES
If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

_____ HOURS

Source: Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH)

Logically Skipped Items

- There has been a need to create data standards for logically skipped items in PRO instruments
- This data standard was defined for the QS (questionnaires) domain in the October 2017 TCG V4.0

Logically Skipped Items

- Section 4.1.1.3, SDTM Domain Specifications, in the TCG says that data from logically skipped items are to be included in QS

Logically Skipped Items

- Case #1:
- If instructions on how to record and/or score responses to logically skipped items are available from the instrument developer, then records for logically skipped items should be included in the submission dataset with the following:

Logically Skipped Items

- QSSTAT = “NOT DONE”
- QSREASND = “LOGICALLY SKIPPED ITEM”
- QSORRES, QSSTRESC, and QSSTRESN are assigned according to the instrument’s instructions

Logically Skipped Items

- Case #2:
- If instructions on how to record and/or score responses to logically skipped items are **not** available from the instrument developer, then records for logically skipped items should be included in the submission dataset with the following:

Logically Skipped Items

- QSSTAT = “NOT DONE”
- QSREASND = “LOGICALLY SKIPPED ITEM”
- QSORRES, QSSTRESC, and QSSTRESN are all set to null

Logically Skipped Items

- Records from logically skipped instrument items should be included in SDTM QS to allow for traceability to the source data (i.e., CRF data, eDiary data)
- Data capture mechanisms may need to be modified to allow for the collection of records for logically skipped items

Logically Skipped Items

- A **sponsor** should be able to distinguish between logically skipped items in an instrument and items with truly missing values
- Those records should be distinguishable in the submitted QS dataset per the data standards defined in TCG Section 4.1.1.3, as well as in corresponding ADaM datasets

Logically Skipped Items

- Recently passed legislation, as well as FDA regulations, call for patient experience data that are well-defined and reliable
- Those well-defined and reliable data should be included in submissions to the FDA
 - This applies to all PRO-related data

Logically Skipped Items

- The FDA expects inclusion of records from logically skipped instrument items as a data standard
- These records are needed for review by clinical and statistical reviewers

Importance of Data Standards (SDTM)

- We have reviewed CDISC SDTM data standards supplements for instruments, such as
 - 4-stair ascend
 - 4-stair descend
 - Rise from floor
 - 10-meter walk
 - CGI, PGI



Importance of Data Standards (ADaM)

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- Imputed endpoint values can be used in primary efficacy endpoint analyses and for sensitivity analyses
- However, discuss with the appropriate review division the appropriate pre-specified imputation method for relevant endpoints
- Records with imputed or observed endpoint values should be clearly identified

Importance of Data Standards (ADaM)

- It's important that missing data values vs. systematic missing values are clearly identifiable
- The amount of missing data can undermine the reliability of clinical findings
- Traceability to SDTM is important

Importance of Data Standards (ADaM)

- Efficacy analysis results are crucial for the regulatory team's review of the drug submission, as well as for product labeling

Importance of Data Standards (ADaM)

Table 14: Change from Baseline in HAQ-DI in Studies PsA-I and PsA-II

	Least Squares Mean Change from Baseline in HAQ-DI at Month 3					
	Nonbiologic DMARD Inadequate Responders ^b (TNF Blocker-Naïve)			TNF Blocker Inadequate Responders ^c		
	Study PsA-I [*]			Study PsA-II [*]		
Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg ^d Twice Daily	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg ^d Twice Daily
N ^a	104	107	104	131	129	132
LSM Change from Baseline	-0.18	-0.35	-0.40	-0.14	-0.39	-0.35
Difference from Placebo (95% CI)	-	-0.17 (-0.29, -0.05)	-0.22 (-0.34, -0.10)	-	-0.25 (-0.38, -0.13)	-0.22 (-0.34, -0.09)

* Subjects received one concomitant nonbiologic DMARD.

^aN is the total number of subjects in the statistical analysis.

^bInadequate response to at least one nonbiologic DMARD due to lack of efficacy and/or intolerability.

^cInadequate response to at least one TNF blocker due to lack of efficacy and/or intolerability.

^dThe recommended dose of XELJANZ is 5 mg twice daily.

In Study PsA-I, the HAQ-DI responder rate (response defined as having improvement from baseline of ≥ 0.35) at Month 3 was 53% in patients receiving XELJANZ 5 mg twice daily, 55% in patients receiving XELJANZ 10 mg twice daily, and 31% in patients receiving placebo. Similar responses were observed in Study PsA-II.

Importance of Data Standards (ADaM)

- Safety results are also crucial for product labeling and in the overall benefit-risk assessment
- There has been an effort to further integrate safety analyses as part of the overall benefit-risk assessment

Importance of Data Standards (SDTM and ADaM)

- PDUFA V, PDUFA VI, and the benefit-risk framework
- Standardized SDTM and ADaM data are crucial for the integrated benefit-risk assessment in regulatory product reviews

BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING

Draft PDUFA VI Implementation Plan (FY 2018-2022)

<https://www.fda.gov/media/84831/download>

<https://www.fda.gov/media/112570/download>



Thank you!

- For specific questions related to study data standards at CDER, email the eData Team
cder-edata@fda.hhs.gov



Back-up slides



Technical Rejection Criteria for Study Data

Technical Rejection Criteria for Study Data

- FDA published “Technical Rejection Criteria for Study Data” which specified the criteria to be used to assess conformance to the required Study Data Standards
- Sponsors must conform to standards in the FDA Data Standards Catalog
 - NDA, BLA, ANDA studies that started after **December 17, 2016**
 - Commercial IND studies that started after **December 17, 2017**

Technical Rejection Criteria for Study Data

- The FDA will implement a process to assess high-level study data standards conformance at the time the submission is submitted and validated
- The FDA will give the industry 90 days' notice on the eCTD website prior to the criteria becoming effective
 - If a submission fails these criteria, it will be rejected, and the sponsor will be notified

Technical Rejection Criteria for Study Data

- There are two high-level validation rules as described in the Technical Rejection Criteria for Study Data
 - ❑ 1734 – TS dataset and correct study start date must be present
 - ❑ 1736 – DM dataset, ADSL dataset and define.xml must be present

CY2018 Conformance Analysis for Validation Errors 1734 and 1736



	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	877	1078	291	649	2895
Total Number Submissions with Critical Errors	195	266	50	113	624
Error 1734	185	186	48	96	515
Error 1736	16	88	2	18	124
Failure Rate (% among submissions with Study Data)	22.2%	24.7%	17.2%	17.4%	21.6%

Notes:

- (1) Analysis includes NDA, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 and 12/31/2018
- (2) Validation of error 1736 is not performed if a study has error 1734
- (3) A submission with multiple studies can report both errors 1734 and 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate
- (4) Analysis is conducted according to the revised TRC (Revised Jan. 2019)

Source: FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)



Summary of Latest Revisions to the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

- **Technical Rejection Criteria for Study Data (Revised 05/01/2018)**
The FDA may refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs, an electronic submission that does not have study data in conformance to the required standards specified in the FDA Data Standards Catalog
- **Technical Rejection Criteria for Study Data (Revised 01/22/2019)**
FDA will not accept an electronic submission that does not have study data in compliance with the required standards specified in the FDA Data Standards Catalog

Source:

FDA Study Data Technical Rejection Criteria (Revised May 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)