

How to Handle the Challenges for the Content of Specific Datasets in FDA Submission for HIV Drugs

Fangfang Du

PHUSE US Connect 2020 - DS04

What covered

- Introduction of HIV
- Summary of specific analysis datasets for HIV drugs
- The regulatory submission process, focus on special FDA requested datasets
- Lesson Learned during the submission process
- Conclusion

About HIV

- What is HIV?
 - HIV infection is a chronic viral infection that, when untreated, causes a progressive destruction of the immune system resulting in acquired immunodeficiency syndrome (AIDS).
- Treatment for HIV
 - Current treatment of HIV consists of a combination of antiretroviral drugs, typically three drugs from two or more classes.
 - The goal of antiretroviral treatment is to indefinitely maintain suppression of plasma HIV-ribonucleic acid (RNA) levels (also called viral load) below the level of detection of sensitive HIV-RNA assays (less than the lower limit of quantification, target not detected).

SUMMARY OF SPECIFIC ANALYSIS DATASETS FOR HIV DRUGS SUBMISSION



- FDA guidance requests the following datasets in CDISC format:

Snapshot Analysis Dataset

- Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment
- CDISC Therapeutic Area Standards User Guide for HIV

Efficacy Outcomes Dataset Adverse Event Analysis Dataset Laboratory Analysis Dataset

- Submitting Select Clinical Trial Data Sets for Drugs Intended To Treat Human Immunodeficiency Virus-1 Infection

HIV-1 Resistance Dataset

- Guidance on Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency: Guidance for Submitting HIV-1 Resistance Data

– **Snapshot Dataset**

- This is the key virologic primary efficacy endpoint analysis that is primarily based on the HIV RNA viral load at a window period visit of interest.
- Due to its importance, CDISC specifically developed a Therapeutic Area Data Standards User Guide for HIV which describes how to use this guide to represent data pertaining to HIV or data commonly collected in HIV trials.

The structure and key variables covered in CDISC Therapeutic Area Standards User Guide for HIV

Summary of the datasets, continued

- **Efficacy Outcomes Data Set (EFFOUT):** a one-record-per-subject data set that contains a comprehensive set of variables pertaining to the subject and their measures of efficacy. The FDA specification organizes these variables into groupings of subject demographics, baseline characteristics (including prior therapies and genotypic and phenotypic data), subject disposition, measures of efficacy over the time span of the trial, exposure, and important covariates
- **Adverse Event Analysis Data Set (ADAEOUT):** a one-record-per-adverse event-per-subject dataset that includes all adverse events reported for a subject during their participation in the trial. Additional variables and specific derivations from the standard ADAE dataset are described. The intent of these additional variables is to aid in the review process.
- **Laboratory Analysis Data Set (LBOUT):** a one-record-per-lab test, -collection, and -subject dataset. The laboratory tests that are most commonly of greatest interest are noted below in the guidance. Additional variables and specific derivations from the standard ADLB dataset are described.

The structure and variables expected are covered in FDA guidance ‘Submitting Select Clinical Trial Data Sets for Drugs Intended To Treat Human Immunodeficiency Virus-1 Infection’.

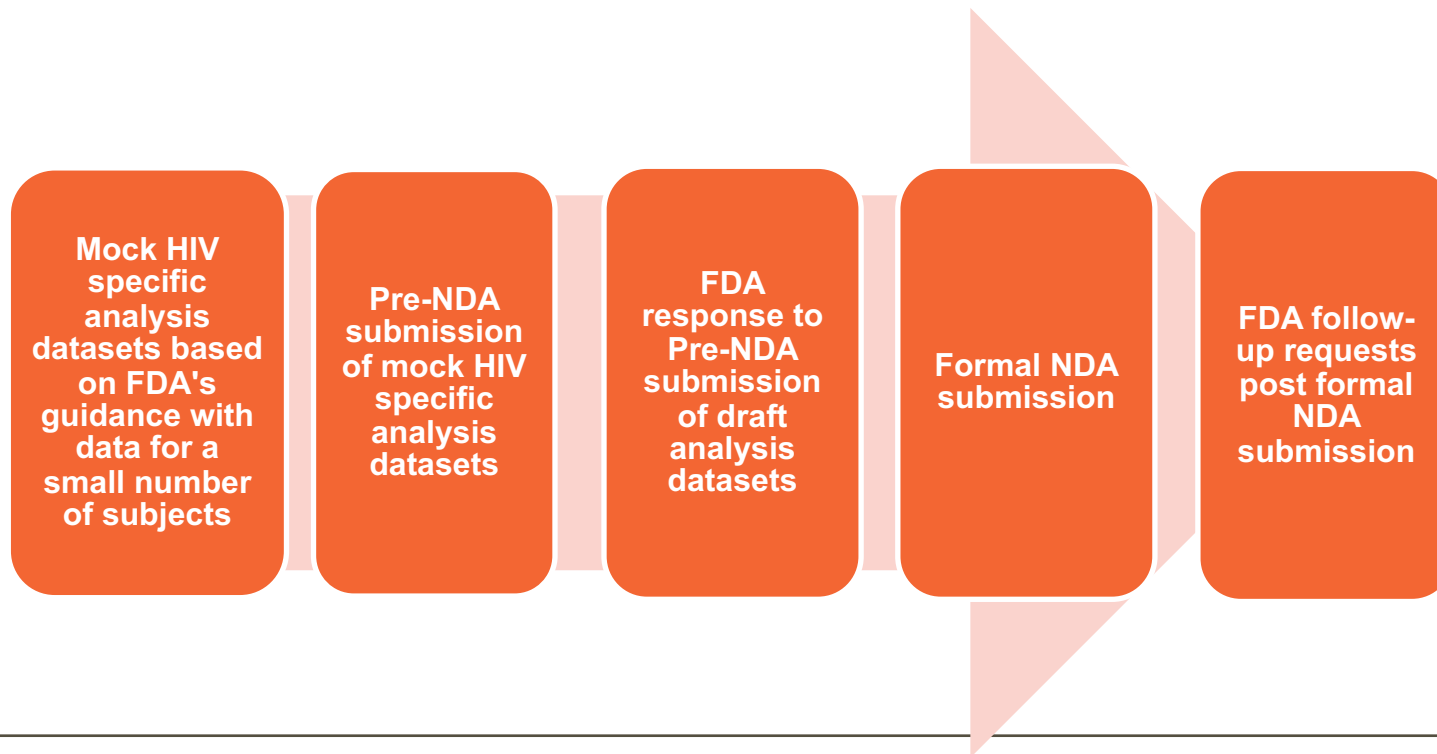
- **HIV-1 Resistance Dataset** is one dataset that combines patient data, endpoint data, genotypic data, and phenotypic data.
- The FDA specification lists the recommended construction of the dataset containing standardization of column headings and variables for HIV-1 Resistance dataset information.

The structure and variables expected are covered in FDA guidance ‘Guidance on Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency: Guidance for Submitting HIV-1 Resistance Data’

Submission process of the study



Only focus on special FDA requested datasets



Step 1: Mock HIV specific analysis datasets based on FDA's guidance with data for a small number of subjects.



- As recommended by ADaM guidance, each project needs to create the required datasets such as ADSL and ADaMs in BDS structure to support safety and efficacy analysis defined in the Report Analysis Plan (RAP).
- In addition, for HIV studies
 - FDA has a list of required variables which may not be required for a specific study based on the data collected and analyzed. In order to aid in the FDA's review process, it is recommended to derive and deliver them to FDA, if possible.
 - Simply following CDISC is not enough, as it may not be up to date with all the information for specific therapeutic area.
 - Carefully following FDA's latest guidance is strongly recommended, even when the information of the dataset duplicates information found in other submitted datasets

Step 1 – Example 1

- FDA has a list of required variables which may not be required for a specific study based on the data collected and analyzed.
- In order to aid in the FDA's review process, it is recommended to derive and deliver them to FDA, if possible.

This table presents example of variables that are recommended in the FDA's guidance for Efficacy Outcomes Dataset.

DSCAEON	Any Ongoing AEs When Study Disc	Char	Expected Values: 'Y', 'N' This variable indicates if there were any AEs that were ongoing at the time of study discontinuation.
DSCAETX	Max Tox Grade of Ongoing AE	Char	Expected Values: '1', '2', '3', '4', '5' The highest toxicity level of any adverse event that was ongoing at the time of study discontinuation.

Step 1 – Example 2

- Per FDA guidance, the information of the dataset duplicates information found in other submitted datasets. It is still required to compile all the variables into these specific datasets.
- For example, even though the information below has been derived in the snapshot analysis dataset, these variables should also be included in the Efficacy Outcomes Dataset since it is listed in the guidance.

Variable Name	Variable Label	Type	Comments
Efficacy Variables for Viral Load Cutoff of 50 copies/mL at Weeks 24, 48, 96, 128, 144 weeks of interest (as applicable).			
V2450FL	Wk 24 Viral Load < 50 copies/mL Flag	Char	Expected Values: 'Y', 'N' Flag variable to indicate whether the viral load at Week 24 was less than 50 copies/mL.
V2450C	Wk 24 Viral Load < 50 copies/mL Category	Char	High level categorization of virologic status from the snapshot algorithm at Week 24, for a cutoff of 50 copies/mL. The values of '1', '2', '3' must be used for this variable with the corresponding definitions:

Step 2: Pre-NDA submission of mock Datasets



- Submit preliminary (or mock) datasets to the Division of Antiviral Products (DAVP) before assembling formal clinical trial datasets
 - FDA could review and feedback on the plans for delivering these datasets to be included in the planned NDA submission.
 - Identify any potential formatting problems as early as possible, the planned datasets will probably contain differences from FDA recommended format due to study differences, this step helped us ensure that the proposals for submission of the datasets were acceptable at the time of FDA pre-NDA submission, especially, Efficacy Outcomes dataset and HIV-1 Resistance dataset.

Step 3: FDA response to Pre-NDA submission of mock analysis datasets



-
- At this step, FDA will provide feedback whether the mock analysis datasets meet expectations and how to improve it to meet the requirement.
 - One lesson learned here is that even though it is acceptable to omit/add variables in the datasets per FDA's guidance, if there are discrepancies with some of the variables and variable names in the proposed mock dataset and those in the standardized HIV dataset requirements document, FDA would like to know the additional details as documentation of why there are discrepancies between FDA's guidance and submitted mock data

Step 3: Example

First table is showing the case where the FDA would not want to see in the comments section for an excluded variable. Second table is a better example of the documentation for why the INVID variable is omitted in the Efficacy Outcomes Analysis dataset.

Variable Name	Variable Label	Type	Comments	Our Specification
INVID	Investigator Identifier	Char		Not Collected

Variable Name	Variable Label	Type	Comments	Our Specification
INVID	Investigator Identifier	Char		Not Collected SDTM IG indicates that this variable is permissible and can be excluded when INVID values are equivalent (1:1) to the SITEID values. No investigators are assigned to multiple sites within this study.

Step 4: Formal NDA submission



- The FDA technical specifications document '*Study Data Technical Conformance Guide*' provides details on the submission of datasets and related files.
 - Components of ADaM CRT Packages
 - XPT datasets
 - DEFINE.xml and style sheets
 - ADaM Reviewers Guide
 - Analysis Results Metadata (Optional but recommended for key displays)
- Ensure Analysis Reviewer's Guide (ADRG) clearly documents the information of these datasets. Especially remember to itemize the added or omitted variables with detailed reason as a separate table.
- These datasets must be accompanied by informative metadata in the form of a compliant Define.xml document that describes the source and derivation of the variables.

Step 5: FDA follow-up requests post NDA submission



- After NDA submission, “unexpected” requests from the FDA after NDA submission may occur.
 - One example: only the phenotypic data for all approved/investigational drug(s) in the same class/protein as the submitted drug is submitted in the HIV-1 Resistance dataset. But post submission, as a part of a follow-up request from FDA, the phenotypic data in all classes were requested by the FDA.

IV. Phenotypic Data:³

For the candidate drug, approved/investigational drug(s) in the same class, and approved/investigational drug(s) outside the candidate drug class with the same target protein (e.g., NNRTIs and NRTIs) or protein complex (e.g., gp120/gp41), sponsors should provide the following data:

- This lesson tells us that while information is collected and could help to aid in the review process, the best practice is to provide sufficient information to facilitate the review process for FDA, even it may not list in the guidance. Thinking what’s behind the requirement and could help to aid in the review process. If not sure, closely communicate with the FDA for clarification.

CONCLUSION



- The FDA requires/recommends that specific additional datasets should be submitted as part of the application for HIV drugs. This assures there is alignment with virology response based on viral load, genotypic and phenotypic data, and to better understand the effects of the new HIV drugs.
- With increasing number of FDA, CDISC, or industry standards becoming available, it is critical to clearly document the proposed solution whenever the FDA's guidance could not be simply followed due to uniqueness of the study.
- Ensure to have close and clear communication with the FDA during every step of the way and be creative and selective in terms of finding the balance between meeting study requirements and remaining compliant with regulatory standards.

- **ACKNOWLEDGMENTS**

The authors greatly appreciate the Clinical Programming team at GSK for their participation in the development of this paper.

- **CONTACT INFORMATION**

Your comments and questions are valued and encouraged. Contact the author at:

Fangfang Du

GSK

1250 S. Collegeville Road

Collegeville, PA 19426

Work Phone: 610-917-4561

Email: fangfang.x.du@gsk.com

Any Questions

