Paper DS04

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

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ABSTRACT

The FDA recommends that specific additional datasets should be submitted as part of the sponsor/applicant's application for drugs intended to treat human immunodeficiency virus (HIV). While the FDA provides detailed guidance and CDISC supplements this with a Therapeutic Area Data Standards User Guide for HIV (TAUG-HIV), there are various factors such as medication, indications and company standards which can impact the submission. This paper provides an overview of the challenges when creating these analysis datasets required for a recent submission of an HIV product, and the approaches utilized to handle the gaps between studies and guidance documents. An alternative approach from the FDA's guidance was developed using the TAUG-HIV to support the SNAPSHOT analysis and the recommended datasets.

INTRODUCTION

HIV infection is a chronic viral infection that, when untreated, causes a progressive destruction of the immune system resulting in acquired immunodeficiency syndrome (AIDS). 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). In clinical trials of antiviral drugs, viral load measurement within the host is collected over time in order to understand the antiviral activity or efficacy of the drug. The collection and association of this data is associated with genotypic and phenotypic changes in viral population. This helps to identify viral characteristics related with treatment failure or success. [1]

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.

While working on the FDA submission for a HIV drug, it is important to closely communicate with FDA in order to meet their expectations and regulatory requirements throughout the process, whilst accurately following all available FDA/CDISC guidance for these specific additional datasets for HIV drugs. This paper will walk through the submission process related to these special analysis datasets for HIV drug and the lessons learned at each step, including the challenges for meeting FDA's requirements, and the solution developed to address comments from both the pre-NDA submission of mock specific datasets and the post regulatory submission.

SUMMARY OF SPECIFIC ANALYSIS DATASETS FOR HIV DRUGS SUBMISSION

Snapshot Analysis Dataset	• Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment [1] • CDISC Therapeutic Area Standards User Guide for HIV [4]
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[3]
HIV-1 Resistance Dataset	• Guidance on Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency: Guidance for Submitting HIV-1 Resistance Data [2]

Figure 1

On the left side of Figure 1 lists the special datasets recommended by the FDA for HIV drugs, and on the right shows the FDA guidance and CDISC supplements used to generate these datasets.

Here is the summary of above 5 datasets:

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

Efficacy Outcomes Data Set is 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. [3]

Adverse Event Analysis Data Set is 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. [3]

Laboratory Analysis Data Set is 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. [3]

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. [2]

The FDA guidance and CDISC supplements provide detailed information and specifications for the content of the above 5 datasets, it also provides an opportunity for dialogue between the sponsor and reviewers to discuss issues with trial design or study conduct which may affect the content of these analysis datasets.

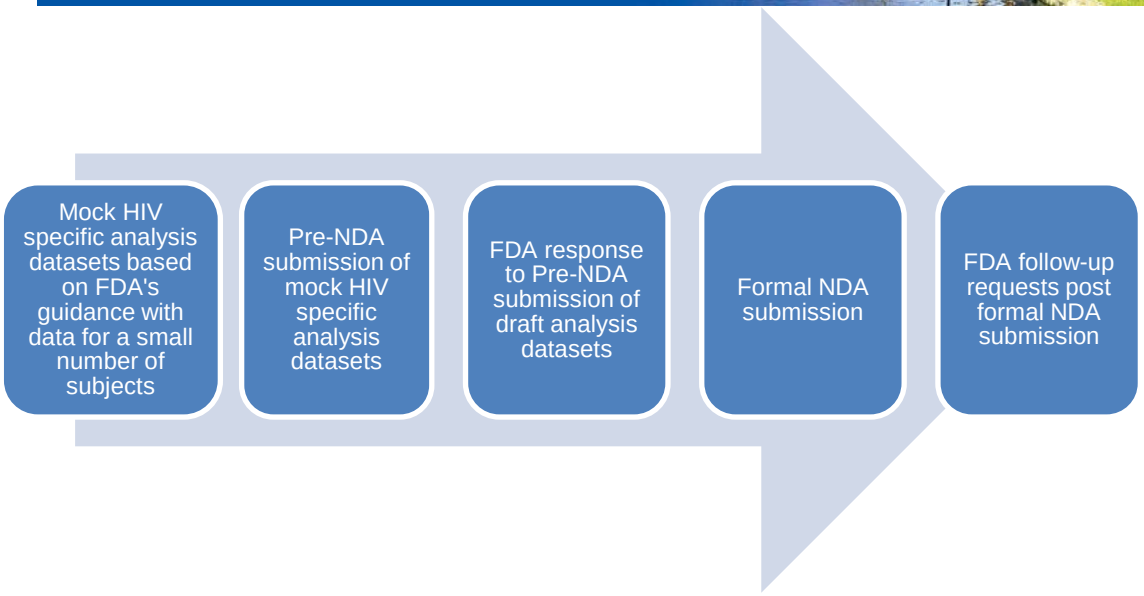

Figure 2

Figure 2 shows the submission process of special FDA requested datasets

LESSION LEARNED

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 required datasets such as ADSL and ADaMs in BDS structure to support safety and efficacy analysis defined in the Report Analysis Plan (RAP). But for HIV studies, the FDA has a list of required variables which may not be required for a specific study based on the data collected and analyzed. When it comes to NDA submissions, especially for a new drug class, simply following CDISC is not enough, as it may not be up to date with all the new drug classes. Carefully following FDA's guidance is strongly recommended, even when variables requested by the FDA are not used in the analyses.

Here are two examples based on FDA dataset specification for the Efficacy Outcomes Dataset:

Example 1: Table 1 presents example of variables that are recommended in the FDA's guidance for Efficacy Outcomes Dataset but may not be required in the analysis per the RAP. In order to aid in the FDA's review process, it is recommended to derive and deliver them to FDA, if possible.

Table 1 [3]

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.

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 in Table 2 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.

Table 2 [3]

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: '1'=Virologic success (HIV-RNA < 50 copies/mL) '2'=Virologic failure '3'=No virologic data
V2450SC	Wk 24 Viral Load < 50 copies/mL Subcat	Char	Further subcategorization of the virologic status from the snapshot algorithm at Week 24, for a cutoff of 50 copies/mL. The values of '1', '2a', '2b', '2c', '2d', '3a', '3b', '3c' must be used for this variable with the corresponding definitions:

Step 2: Pre-NDA submission of mock Efficacy Outcomes Dataset and HIV-1 Resistance Dataset
To identify any potential formatting problems as early as possible, all sponsors are encouraged to submit preliminary (or mock) Efficacy Outcomes dataset and Resistance dataset to the Division of Antiviral Products (DAVP) before assembling formal clinical trial datasets, So FDA could review and feedback on the plans for delivering these two datasets to be included in the planned NDA submission. In the guidance, FDA has advised to seek DAVP's consultation if considering an alternative approach to any recommended column headings, variables or definitions reflected in current FDA Guidance documents. Although these datasets are being planned with substantial consideration given to the current FDA Guidance documents, the planned datasets will probably contain differences from FDA recommended format due to study differences. Some of the proposed format differences are necessitated by unique attributes of the study, others are associated with study design features. So, please make sure proposals for submission of the Efficacy Outcomes dataset and HIV-1 Resistance dataset are acceptable at the time of FDA pre-NDA submission.

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

Table 3 below is showing the case where the FDA would not want to see in the comments section for an excluded variable. Table 4 is a better example of the documentation for why the INVID variable is omitted in the Efficacy Outcomes Analysis dataset.

Table 3

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

Table 4

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. The same rules should be followed for all ADaM datasets, including these 5 datasets. Just a reminder, please make sure 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. Additionally, 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" request from the FDA after NDA submission may occur. Here is one example,

Table 5 [2]

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:

By following section 4 of the guidance for HIV-1 Resistance Dataset in Table 5, only the phenotypic data for all approved/investigational drug(s) in the same class/protein as the submitted drug is required in the HIV-1 Resistance dataset.

But post submission, as a part of a follow-up request from FDA, the phenotypic data of approved/investigational drug(s) in all classes were requested by the FDA. 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

Regulatory submission is always a daunting task for any company who are looking to put a new drug onto the market. This is the last critical step after tremendous amounts of time, money and effort from many people dedicated to this new drug with the hope to help save many lives who are suffering from this disease. It doesn't matter how much prior experience we have with NDA submissions, each road to successful drug approval is unique since every drug/study is unique.

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.

Hope this paper will benefit future projects seeking to implement and govern end-to-end standards for HIV drugs.

REFERENCES

[1] Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-immunodeficiency-virus-1-infection-developing-antiretroviral-drugs-treatment

[2] Guidance on Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency, available at: https://www.fda.gov/media/88255/download

[3] Submitting Select Clinical Trial Data Sets for Drugs Intended To Treat Human Immunodeficiency Virus-1 Infection, available at: https://www.fda.gov/media/112667/download

[4] CDISC Therapeutic Area Standards User Guide for HIV, available at: https://www.cdisc.org/standards/therapeutic-areas/hiv/hiv-therapeutic-area-user-guide-v10

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