Attachment to

Guidance on Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency

Guidance for Submitting HIV Resistance Data

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Contains Nonbinding Recommendations

GUIDANCE FOR SUBMITTING HIV RESISTANCE DATA

Sponsors are encouraged to use the following sample format for submitting HIV resistance data.

One dataset combines patient data, endpoint data, genotypic data, and phenotypic data. There are a number of ways datasets can be subdivided (i.e., by clinical study, baseline isolates, or virologic failure isolates) and this should be discussed with the division before submission.

For each study, we recommend constructing datasets as SAS transport files containing the following information:

- One record (row) per patient per isolate (e.g., baseline, failure, and other time points).
- Data in columns (with suggested column headings shown below)[1] on all isolates.
- Genotypic data should be provided on the corresponding record for each patient isolate for baseline isolates of all patients in treatment-experienced studies and the endpoint isolates of virologic failures and discontinuations in all studies.[2] In treatment-naïve studies, a baseline sample should be collected and stored from all patients for future phenotypic and genotypic analysis of virologic failures.
- Phenotypic data should be provided on the corresponding record for each patient isolate for baseline isolates and the endpoint isolates of virologic failures and discontinuations.[2] In treatment-experienced studies, it is recommended that baseline phenotypic data be obtained for all patients.

The specific criteria for defining virologic failures should be discussed with the division and may include multiple primary and secondary protocol endpoints. The endpoints for clinical virologic and resistance outcome analyses should be consistent.

Information to Include with Suggested Column Headings[1]

I. Patient Data:

- Patient identification number (ID number should be unique for all studies)
- Isolate (e.g., baseline, week 24, week 48, discontinuation. Multiple isolates should be numbered.)
- Date of isolate
- Study day (number of days since the patient started the study product)
- Previous therapeutic products where available
- Treatment group
- Censored for analysis (yes or no)

[1] In the SAS transport files, column headings can be given abbreviated column names to fit the SAS format; however, it is suggested that a description of column names be provided to the reviewer in the submission.

[2] Treatment and endpoint samples should be collected when the patient is still on the study product.

II. Endpoint Data:

- HIV RNA (copies/mL) at baseline
- HIV RNA (copies/mL) at predefined time points (e.g., week 24 and week 48), one column for each time point including baseline (i.e. the viral load throughout the course of the study is provided for each sample)
- HIV RNA (copies/mL) at other times (e.g., loss of virologic response or discontinuation because of adverse event)
- Endpoint assessment (e.g., mean log change in viral load from baseline)
- Other endpoint assessments (e.g., DAVG)
- Indication of data were censored for reasons other than virologic failure (e.g., discontinuation because of adverse event)
- Outcome (i.e. responder, virologic failure, discontinuation while suppressed, discontinuation before achieving viral suppression)
- Reason for discontinuation (i.e., adverse event, pregnancy) or failure (i.e., never suppressed, rebound)
- HIV RNA (copies/ml) from additional time points can be included

III. Genotypic Data:[3]

- Clade
- Genotype for the RT, protease and gp160 (for products targeting entry only), one amino acid per column with the wild-type (WT) amino acid as column heading. Changes from WT standard sequence indicated (i.e., blanks indicate no change).
- Column with total number of PI mutations in patient isolate (for baseline and endpoint isolates). The specific mutations to include should be discussed with the division in advance.
- Column with total number of NRTI mutations in patient isolate (for baseline and endpoint isolates). The specific mutations to include should be discussed with the division in advance.
- Column with total number of NNRTI mutations in patient isolate (for baseline and endpoint isolates). The specific mutations to include should be discussed with the division in advance.

Example (Table 1 highlights how genotype information can be displayed, but does not include all column headings previously suggested.)

[3] Genotypic data should be provided for baseline isolates of all patients in treatment-experienced studies and the endpoint isolates of virologic failures and discontinuations in all studies. In treatment-naïve studies, a baseline sample should be collected and stored from all patients for future phenotypic and genotypic analysis of virologic failures.

Table 1. Example of Genotype Information Display

Patient #	Isolate	V-82	N-83	I-84	I-85	G-86	R-87	N-88	L-89	L-90	# PI Mutations
001	BL							S		M/L	2
001	WK48			V				S		M	3
002	BL	A/T		V				D		M	4
002	WK48	T		V						M	3
003	BL	T		V							2
004	BL			V						M	2

BL = baseline
WK48 = week 48 for investigational product

IV. Protease Cleavage Sites (for protease inhibitors only):

- NC/p1 Gag cleavage sites: show amino acid and position of cleavage site of WT in column headings (as above for genotype) and indicate amino acid change if mutant
- p1/p6 Gag cleavage sites: show amino acid and position of cleavage site of WT in column headings (as above for genotype) and indicate amino acid change if mutant

V. Phenotypic Data:[4]

1. *Information on the investigational product*
   - Baseline EC_{50} value for investigational product
   - Baseline EC_{50} value of reference strain for investigational product
   - Fold resistant change of baseline EC_{50} value compared to EC_{50} value of reference strain of investigational product
   - EC_{50} value at time of endpoint assessment or failure for investigational product
   - Fold change in EC_{50} value at time of endpoint assessment or failure compared to reference strain for investigational product
   - Fold change in EC_{50} value at time of endpoint assessment or failure compared to baseline for investigational product
   - Replication capacity (if available)

2. *Information on approved and other investigational anti-HIV products (if available) in the same class*
   - Fold change in EC_{50} value of baseline compared to reference strain for each of the approved and other investigational anti-HIV products (if available)
   - Fold change in EC_{50} value at time of endpoint assessment or failure compared to reference strain for each of the approved and other investigational anti-HIV products (if available)
   - Fold change in EC_{50} value at time of endpoint assessment or failure compared to baseline for each of the approved and other investigational anti-HIV products (if available)

[4] Phenotypic data should be provided for baseline isolates and the endpoint isolates of virologic failures and discontinuations. In treatment-experienced studies, it is recommended that baseline phenotypic data be obtained for all patients.

3. *Information on approved and other investigational products (if available) outside the investigational product's class with same target protein (e.g., NRTIs and NNRTIs)*
   - Fold change in EC_{50} value of baseline compared to reference strain for approved and other investigational products (if available) outside the investigational product's class
   - Fold change in EC_{50} value at time of endpoint assessment or failure compared to reference strain for each of the approved and other investigational products (if available) outside the investigational product's class
   - Fold change in EC_{50} value at time of endpoint assessment or failure compared to baseline for each of the approved and other investigational products (if available) outside the investigational product's class

4. *Information on other antiretroviral products in the regimen*
   - Fold change in EC_{50} value of baseline compared to reference strain for other antiretroviral products in the regimen, one column per product
   - Fold change in EC_{50} value at time of endpoint assessment or failure compared to reference strain for other antiretroviral products in the regimen, one column per product
   - Fold change in EC_{50} value at time of endpoint assessment or failure compared to baseline for other antiretroviral products in the regimen, one column per product

Example (Table 2 highlights how phenotype information can be displayed, but does not include all column headings previously suggested.)

Table 2. Example of Phenotype Information Display

	Agent X				Other Agents in the Same Class*		Other Agents Outside Agent Class*	
Sample	EC_{50} value Agent X	Ref strain EC_{50} value Agent X	Δ resis from ref Agent X	Δ resis from BL Agent X	Δ resis from ref Agent Y	Δ resis from BL Agent Y	Δ resis from ref Agent A	Δ resis from BL Agent A
Baseline								
Endpoint								

Agent X = candidate agent

Δ resis = fold resistance change, e.g.: $\frac{EC_{50} \text{ value of sample with Agent X}}{EC_{50} \text{ value of reference (or baseline) strain with Agent X}}$

Ref strain = reference strain (or WT)

Endpoint = predefined time point for endpoint assessment (e.g., week 24, week 48, failure or discontinuation)

*Note: The Δ resis from ref and Δ resis from BL should be included for all approved anti-HIV products

VI. Co-Receptor Usage (for all agents targeting co-receptors):

- Co-receptor usage of baseline isolates. Indicate R5, X4, D for dual-tropic, M for mixed-tropic, or D/M if the assay cannot distinguish between dual or mixed, in a column.
- Baseline R5 tropism assay value (e.g., RLUs).
- Baseline X4 tropism assay value (e.g., RLUs).

- Co-receptor usage of virologic failures and end-of-study isolates (on therapy). Indicate R5, X4, D for dual-tropic, M for mixed-tropic, or D/M if the assay cannot distinguish between dual or mixed, in a column.
- R5 tropism assay value at failure or end of study (e.g., RLUs).
- X4 tropism assay value at failure or end of study (e.g., RLUs).

VII. Therapeutic Drug Monitoring Data (when available):

- Patient's C_{min}
- Serum adjusted IQ (inhibitory quotient = C_{min}/serum adjusted EC_{50} value)