Attachment to

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

Guidance for Submitting HCV 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 HCV RESISTANCE DATA

Sponsors are encouraged to use the following sample format for submitting HCV 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 for baseline isolates and the endpoint isolates of virologic failures and discontinuations[2] — on the corresponding record for each patient isolate.
- Phenotypic data for baseline isolates and the endpoint isolates of virologic failures and discontinuations[2] — on the corresponding record for each patient isolate. We recognize the difficulty of phenotypic analysis of HCV. Sponsors are strongly encouraged to appropriately collect and store samples for later analysis if warranted. If the pathway to resistance as defined by genotypic analysis is straightforward, phenotypic analysis may not be necessary. We recommend that sponsors consult with the division to determine whether phenotypic analysis should be conducted.

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] Samples should be collected from rebound and failure isolates for analysis when the patient is receiving the study product.

II. Endpoint Data:

- HCV RNA (log_{10} copies/mL) at baseline
- HCV RNA (log_{10} copies/mL) at predefined time points (e.g., week 24 and week 48), one column for each time point including baseline
- HCV RNA (log_{10} copies/mL) at time of loss of virologic response or discontinuation because of adverse event
- Endpoint assessment (e.g., log_{10} change in viral load from baseline)
- Follow-up for determination of sustained virologic response
- Indication of data were censored for reasons other than virologic failure (e.g., discontinuation because of adverse event)
- HCV RNA (log_{10} copies/ml) from additional time points can be included

Note: We recommend that sponsors analyze HCV RNA with a sensitive and specific HCV RNA assay with lower limits of quantification in the range of less than 100 copies/mL (IU/mL).

III. Genotypic Data:

- HCV subtype (e.g., 1a, 1b, 2)
- Genotype information for all the replicases or relevant coding region sequenced, one amino acid per column with the wild-type (WT) amino acid as column heading identified using the one amino acid abbreviation. Changes from WT standard sequence indicated (i.e., blanks indicate no change) and known polymorphisms are indicated with an asterisk.

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

Table 1. Example of Genotype Information Display

Patient #	Isolate	Subtype	E414	F415	D416	L417
001	BL	1				
001	WK48	1		Y		
001	FU	1				
002	BL	1				
002	WK48	1		Y		
002	FU	1		Y		

BL = baseline
WK48 = week 48
FU = follow-up

IV. Phenotypic Data:

1. *Information on the investigational product*
   - Baseline EC_{50} value for investigational product
   - EC_{50} value of reference strain for investigational product (a widely available standard laboratory strain is recommended as the reference strain)

- Fold 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 values 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
- EC_{50} value at follow-up for investigational product
- Fold change values in EC_{50} value at follow-up compared to reference strain for investigational product
- Fold change in EC_{50} value at follow-up compared to baseline for investigational product

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

Example (Table 2 highlights how phenotype information can be displayed.)

Table 2. Example of Phenotype Information Display

	Agent X				Other Agents in Same 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
Baseline						
Endpoint						

Agent X = candidate agent
BL = baseline
Endpoint = predefined time point for endpoint assessment (e.g. week 24, week 48, failure or discontinuation)
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)
*Note: The Δ resis from ref and Δ resis from BL should be included for all approved and other investigational anti-HCV products (if available)