
Attachment to

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

Guidance for Submitting HBV Resistance Data

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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

**June 2006
Clinical Antimicrobial**

Contains Nonbinding Recommendations

GUIDANCE FOR SUBMITTING HBV RESISTANCE DATA

Sponsors are encouraged to use the following sample format for submitting HBV 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 of all patients and the endpoint isolates of virologic failures and discontinuations² — on the corresponding record for each patient isolate.
- Phenotypic data for baseline isolates and the endpoint isolates of virologic failures and discontinuations² — on the corresponding record for each patient isolate. We recognize the difficulty of phenotypic analysis of HBV. 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 (e.g., lamivudine), 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 Headings¹

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.

Contains Nonbinding Recommendations

II. Endpoint Data:

- HBV DNA (log₁₀ copies/mL) at baseline
- HBV DNA (log₁₀ copies/mL) at predefined time points (e.g., week 24 and week 48), one column for each time point including baseline
- HBV DNA (log₁₀ copies/mL) at time of loss of virologic response or discontinuation because of adverse event
- Endpoint assessment (e.g., log₁₀ change in viral load from baseline)
- Indication of data were censored for reasons other than virologic failure (e.g., discontinuation because of adverse event)
- HBV DNA (log₁₀ copies/ml) from additional time points can be included

Note: We recommend that sponsors analyze HBV DNA with a sensitive and specific HBV DNA assay with a lower limit of quantification less than 1,000 copies/mL.

III. Genotypic Data:

- HBV subtype
- Genotype information for all the RT 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 the baseline sequence should be indicated (i.e., blanks indicate no change) and known polymorphic amino acid residues flagged in the column heading.

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

Table 1. Example of Genotype Information Display

Patient #	Isolate	Subtype	rtY203	rtM204	rtD205	rtD206
001	BL	A				
001	WK48	A		V		
002	BL	C				
002	WK48	C		I		
003	BL	A				
004	BL	B		V		

BL = baseline

WK48 = week 48

IV. Phenotypic Data:

1. Information on the investigational product

- Baseline EC₅₀ value for investigational product
- EC₅₀ value of reference strain for investigational product (a widely available standard laboratory strain is recommended as the reference strain)
- Fold change of baseline EC₅₀ value compared to EC₅₀ value of reference strain of investigational product

Contains Nonbinding Recommendations

- EC₅₀ value at time of endpoint assessment or failure for investigational product
 - Fold change values in EC₅₀ value at time of endpoint assessment or failure compared to reference strain for investigational product
 - Fold change in EC₅₀ value at time of endpoint assessment or failure compared to baseline for investigational product
2. *Information on approved and other investigational anti-HBV products (if available)*
- Fold change in EC₅₀ value of baseline compared to reference strain for each of the approved and other investigational anti-HBV products (if available)
 - Fold change in EC₅₀ value at time of endpoint assessment or failure compared to reference strain for each of the approved and other investigational anti-HBV products (if available)
 - Fold change in the EC₅₀ value at time of endpoint assessment or failure compared to baseline for each of the approved and other investigational anti-HBV products (if available)

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

Sample	Agent X				Other Agents in Same Class*	
	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., $\frac{\text{EC}_{50} \text{ value of sample with Agent X}}{\text{EC}_{50} \text{ value of reference (or baseline) strain with Agent X}}$

EC₅₀ 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-HBV products (if available).