Attachment to

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

Guidance for Submitting HBV Resistance Data

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

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Clinical Antimicrobial
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 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 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 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)

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\(^1\) 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 (log_{10} copies/mL) at baseline
- HBV DNA (log_{10} copies/mL) at predefined time points (e.g., week 24 and week 48), one column for each time point including baseline
- HBV DNA (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)
- Indication of data were censored for reasons other than virologic failure (e.g., discontinuation because of adverse event)
- HBV DNA (log_{10} 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>
<thead>
<tr>
<th>Table 1. Example of Genotype Information Display</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>001</td>
</tr>
<tr>
<td>001</td>
</tr>
<tr>
<td>002</td>
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<tr>
<td>002</td>
</tr>
<tr>
<td>003</td>
</tr>
<tr>
<td>004</td>
</tr>
</tbody>
</table>

BL = baseline
WK48 = week 48

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
Contains Nonbinding Recommendations

- EC\textsubscript{50} value at time of endpoint assessment or failure for investigational product
- Fold change values in EC\textsubscript{50} value at time of endpoint assessment or failure compared to reference strain for investigational product
- Fold change in EC\textsubscript{50} 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 EC\textsubscript{50} value of baseline compared to reference strain for each of the approved and other investigational anti-HBV products (if available)
- Fold change in EC\textsubscript{50} 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 EC\textsubscript{50} 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>
<thead>
<tr>
<th>Sample</th>
<th>Agent X</th>
<th>Other Agents in Same Class*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC\textsubscript{50} value</td>
<td>Ref strain from ref</td>
</tr>
<tr>
<td></td>
<td>Agent X value</td>
<td>EC\textsubscript{50} from ref</td>
</tr>
<tr>
<td></td>
<td>Agent X</td>
<td>Agent X</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td></td>
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</tr>
</tbody>
</table>

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., EC\textsubscript{50} value of sample with Agent X
Δ resis from ref = fold resistance change, e.g., EC\textsubscript{50} value of reference (or baseline) strain with Agent X

*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).