Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Aimee Hodowanec at 240-402-5752.

U.S. Department of Health and Human Services
Food and Drug Administration
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Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of chronic hepatitis D virus (HDV) infection.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current recommendations regarding the overall development program and clinical trial designs for the development of drugs and biologics to support an indication for the treatment of chronic HDV infection.

FDA encourages sponsors to communicate with the Division of Antiviral Products (DAVP) through the pre-investigational new drug application (pre-IND) consultation program to discuss the development of drugs with unique considerations based on mechanism of action, novel treatment approaches, or the use of novel biomarkers.[3] This draft guidance is intended to serve as a focus for continued discussions among DAVP, pharmaceutical sponsors, the academic community, and the public.[4]

This guidance focuses on considerations that are specific to HDV drug development. General topics in early phase drug development, statistical analysis, and clinical trial design are addressed in the International Conference on Harmonisation (ICH) guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related*

[1] This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *drug* includes both human drugs and therapeutic biological products unless otherwise specified.

[3] See the FDA's Getting Started with the Division of Antiviral Products Pre-IND Process web page at https://www.fda.gov/drugs/pre-ind-consultation-program/getting-started-division-antiviral-products-pre-ind-process.

[4] In addition to consulting FDA guidances, sponsors are encouraged to contact DAVP to discuss specific issues that arise during the development of drugs for the treatment of HDV infection.

Issues in Clinical Trials (May 2001).[5] The draft guidance for industry *Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment* (November 2018) also contains information that is relevant to HDV drug development.[6]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

HDV is a replication-defective virus that uses the hepatitis B virus (HBV) surface antigen (HBsAg) as its envelope protein. Therefore, HDV infection only occurs in the setting of concurrent HBV infection (Wranke and Wedemeyer 2016). According to the World Health Organization, an estimated 15–20 million people worldwide are living with HBV/HDV co-infection.[7] Subsequently, a meta-analysis reported a much higher worldwide HBV/HDV co-infection prevalence of 62–72 million (Chen et al. 2019). Areas of high HDV prevalence include Eastern and Mediterranean Europe, the Middle East, Central and North Asia, the Amazon basin, and parts of Africa (Chen et al. 2019). HDV prevalence is thought to be relatively low in the United States overall, but may be increased in certain subpopulations, such as in persons who inject drugs and in persons born in, or who have lived in, countries where the disease is endemic. Population-based data from the National Health and Nutrition Examination Survey estimated that the anti-HDV antibody prevalence among adults in the United States is 0.15 percent (Patel et al. 2019). There are eight recognized genotypes of HDV (1 to 8); the globally prevalent genotype 1 is the predominant genotype in the United States.

Relative to HBV monoinfection, HBV/HDV co-infection may be associated with more severe liver disease, leading to increased rates of cirrhosis, hepatocellular carcinoma, hepatic decompensation, and liver failure (Fattovich et al. 1987; Romeo et al. 2009). Although currently available HBV therapies are effective in suppressing HBV replication, the rate of HBsAg loss remains low (Tang et al. 2018). In the absence of HBsAg loss, HDV infection persists. Therefore, therapies directly targeting HDV may be of clinical benefit. At present there are no drugs approved for the treatment of chronic HDV infection, although pegylated interferon-alpha (PEG-IFN-α) is commonly used. However, PEG-IFN-α is associated with significant toxicity and sustained virologic response rates (defined as undetectable HDV RNA levels 6 months after

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] See the World Health Organization's Hepatitis D web page at https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-d.

treatment) of only 25 to 30 percent (Erhardt et al. 2006; Wedemeyer et al. 2011). In addition, late virologic relapses are common following treatment with PEG-IFN-α, and it is not known if HDV sustained clearance can be achieved in the setting of persistent HBsAg positivity (Heidrich et al. 2014).

Because chronic HDV infection is considered serious and life-threatening and there are no approved treatments, investigational anti-HDV drugs may be eligible for FDA's expedited programs, such as fast track, breakthrough therapy, and priority review designations.[8]

III. DEVELOPMENT PROGRAM

A. General Drug Development Considerations

This section discusses nonclinical and early phase clinical development considerations, including the evaluation of antiviral activity and resistance, issues related to the target population for drug development, and safety considerations.

1. Early Phase Development Considerations

Early clinical evaluation should provide sufficient data to establish safety and antiviral activity in support of phase 3 trials.

a. Pharmacology/toxicology development considerations

Sponsors should refer to the following guidance documents for nonclinical development considerations:

- Guidance for industry *Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment*
- ICH guidance for industry *M3(R2) Nonclinical Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010)
- ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012)
- ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996)

b. Nonclinical virology development considerations

Sponsors should consider recommendations for general antiviral and HBV drug development addressed in the guidances for industry *Antiviral Product Development — Conducting and*

[8] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014).

Submitting Virology Studies to the Agency (June 2006), and *Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment*, including recommendations for studies of mechanism of action, determination of antiviral activity in cell culture, cytotoxicity, and mitochondrial toxicity.

Sponsors should also consider the following recommendations specific for HDV drug development:

- Antiviral activity determination in cell culture: To assess the breadth of activity of the investigational drug, the effective drug concentration at which virus replication is inhibited by 50 and 90 percent (EC_{50} and EC_{90} values) should be determined against different genotypes of HDV, including genotype 1, in cell culture. If EC_{50} values vary significantly across genotypes, indicating a lack of conservation of the drug target, the breadth of activity against genotype 1 should also be determined by testing multiple geographically and temporally distinct isolates of this genotype.

- Cell culture combination antiviral activity: Cell culture combination antiviral activity of an investigational drug against HDV should be determined with approved drugs for HBV and for HDV (when anti-HDV drugs are approved) to determine the likelihood of antagonism when used in combination for the treatment of HBV/HDV infection. Sponsors should assess the effect of approved drugs for HBV on the activity of the investigational HDV drug, and conversely, the effect of the investigational HDV drug on the activity of approved HBV drugs.

- Activity in animal models:[9] Animal models of HDV infection may be important for assessing the antiviral activity of investigational drugs, given the difficulty in propagating the virus in cell culture. Sponsors should consider the following recommendations related to animal models:

  - Animal models for consideration may include immunocompromised mice with chimeric human/mouse livers and transgenic mice expressing human sodium taurocholate cotransporting polypeptide (NTCP) receptor and HBsAg (Winer et al. 2018). The woodchuck model using HDV pseudotyped with woodchuck hepatitis virus envelope proteins can be considered for drugs that do not specifically target the HDV/HBV envelope protein or human NTCP receptor (Aldabe et al. 2015).

  - If studies are conducted in animal models to support an HDV treatment program, we recommend including time course plots of viral load (RNA) and antigen expression data for each animal. We recommend testing different HDV/HBV genotypes and assessing resistance development where feasible.

- Evaluating HDV resistance: FDA encourages sponsors to investigate resistance in nonclinical models of infection where feasible, although such studies may be challenging

[9] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

given the limitations of propagating HDV in cell culture and animal models and the dependency of HDV on HBV envelope proteins for infection.

- Evaluating HDV cross-resistance: If a drug for treatment of HDV infection is approved and HDV variants resistant to the drug are identified, these variants should be assessed for susceptibility to the investigational drug. Likewise, HDV variants resistant to the investigational drug should be assessed for susceptibility to any approved drugs for HDV.

c. Clinical pharmacology development considerations

Studies to characterize pharmacokinetics including the effect of extrinsic (e.g., drug-drug interaction studies, food effect studies) and intrinsic factors (e.g., pharmacokinetic studies in subjects with renal impairment or hepatic impairment) should be conducted early in development to inform the trial design for phase 2 and phase 3 trials. Sponsors should consider recommendations in the pertinent guidances for industry.

d. Efficacy considerations

In early clinical trials, the sponsor should measure HDV RNA levels during a short treatment period (i.e., one to three months, depending on the drug's mechanism of action) to assess activity. The sponsor should assess changes in alanine aminotransferase (ALT) as a key secondary endpoint.

2. Drug Development Population

Development programs should include a diverse and representative clinical trial population, and sponsors should consider the following points related to trial populations:

- HDV infection is a global disease with the greatest burden of infection occurring in Eastern and Mediterranean Europe, the Middle East, the Amazon Basin, and parts of Asia and Africa.

  – Under 21 CFR 312.120, FDA will accept data from a well-designed, well-conducted, non-IND foreign trial as support for an IND or application for marketing approval if the trial was conducted in accordance with good clinical practice and if FDA is able to validate the data from the trial through an onsite inspection, as necessary.[10]

  – Although foreign data may be acceptable as a sole basis for marketing approval under certain circumstances (see 21 CFR 314.106), FDA encourages sponsors to include U.S. patients in development programs to provide additional experience relevant to the U.S. population.

[10] For additional information, see the guidance for industry and FDA staff *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions* (March 2012).

- FDA encourages sponsors to discuss their enrollment strategies and plans for phase 2 and phase 3 trials with DAVP. Eligibility criteria should allow the clinical trial population to reflect the diversity of the patients who will be using the drug if the drug is approved.[11]

- Sponsors should conduct initial trials to define antiviral activity and dose-response in patients without cirrhosis or with compensated cirrhosis, as these patients are at lower risk of imminent clinical progression or decompensation. In the later stages of drug development, enrollment of patients with decompensated liver disease may be considered (see section III.B.2., Trial Population).

- In the absence of a serious safety signal in adults, it may be appropriate to enroll adolescent patients (for the purpose of this guidance, ages 12 to younger than 18 years of age) concurrently with adults in phase 3 trials and to make every effort to obtain confirmatory pharmacokinetic and safety data from a cohort in this age group as part of the data included at the time of filing of the original new drug application or biologics license application.

3. Safety Considerations

An initial marketing application should include adequate safety data, such as the following, to allow for a benefit-risk assessment of the drug:

- Safety data from 300 to 500 patients exposed to the proposed drug dose and treatment duration (or greater) may be adequate; however, the size of the safety database could be smaller for investigational drugs that demonstrate substantial efficacy and safety compared to available therapies. Nonclinical or clinical safety signals may necessitate a larger safety database or the conduct of additional safety studies. For a drug approved for use in patients without cirrhosis or with compensated cirrhosis, the safety database needed to extend use of the drug to the decompensated cirrhotic population would depend on the safety profile of the investigational drug and the overall benefit-risk profile for the indicated population.

- Clinical trial protocols should include predefined algorithms for data collection in the setting of significant hepatic events, such as ALT flares or reactivation of HDV or HBV. FDA encourages use of an independent adjudication committee to evaluate significant hepatic events to determine whether the events represent drug-related toxicity, flares related to viral reactivation, or immunologic responses to virologic infection.

- Severe acute exacerbations of HDV and HBV infection may occur after antiviral therapy is discontinued. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-HDV and/or anti-HBV therapy. In certain circumstances, resumption of antiviral therapy may be warranted. The sponsor should adequately monitor and evaluate these concerns in the

[11] For additional information, see the draft guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (June 2019). When final, this guidance will represent the FDA's current thinking on this topic.

development program and convey, as appropriate, these concerns in proposed drug labeling.

B. Phase 3 Efficacy Trial Considerations

1. Trial Design

No drugs have been approved for the treatment of chronic HDV infection. Therefore, a double-blind, placebo-controlled trial is the FDA's preferred trial design for a phase 3 clinical trial.

Alternative trial design options include the following:

- Three-arm, randomized, controlled trial comparing investigational drug, standard-of-care treatment, and placebo.
  - Although PEG-IFN-α has not been approved by FDA for the treatment of chronic HDV infection, it is used in clinical practice and is considered the standard-of-care in some parts of the world. As such, the use of PEG-IFN-α as a comparator in a clinical trial may be acceptable. However, the treatment effect of PEG-IFN-α over placebo has not been well established; therefore, superiority of the investigational drug versus placebo should be demonstrated to support efficacy. The comparison between PEG-IFN-α and placebo can establish the effect of PEG-IFN-α, and the comparison between the investigational drug and PEG-IFN-α can help to evaluate the efficacy and the safety profile of the investigational drug.
- Randomized, controlled trial in which subjects are randomized to the investigational drug (immediate treatment group) or placebo for a prespecified duration followed by open label treatment with investigational drug (deferred treatment group). Effectiveness would be demonstrated by showing an early significant improvement over the placebo control.
- Randomized, controlled superiority trial comparing the investigational drug plus standard-of-care treatment to standard-of-care treatment alone (i.e., an add-on trial). In this case, although effectiveness is demonstrated, it would have been shown only when the investigational drug is added to the standard-of-care treatment; the sponsor would not know whether the investigational drug has an effect when used alone.
- Randomized, controlled superiority trial comparing different doses and/or durations of the investigational drug.

After approval of a drug for the treatment of HDV infection, a randomized, controlled superiority or noninferiority trial comparing the investigational drug against an active comparator is appropriate.

2. Trial Population

Sponsors should include the following virologic and clinical characteristics in patient eligibility criteria:

- Documentation of chronic HDV infection, defined as positive serum anti-HDV antibodies
- Quantifiable HDV RNA of at least 6-month duration
- Receiving HBV treatment in accordance with current treatment guidelines. Patients who qualify for HBV treatment should be on a stable regimen for at least 3 months with documented HBV DNA suppression before initiating the HDV investigational therapy.

Sponsors should enroll sufficient numbers of patients in the trials who are infected with HDV genotype 1 to assess efficacy in this population.

Sponsors should consider the following when enrolling patients without cirrhosis or with compensated cirrhosis:

- The presence or absence of cirrhosis at trial entry should be documented. The use of a noninvasive modality to define the presence or absence of cirrhosis in a trial should be supported by references that summarize the performance characteristics and sensitivity and specificity of the modality for its intended purpose in the proposed population.
- FDA recommends that sponsors exclude patients with decompensated cirrhosis or a history of any prior hepatic decompensation event until data on the safety and effectiveness of a given therapy in patients without cirrhosis and with compensated cirrhosis are obtained.

3. Randomization and Stratification

If multiple subpopulations are included in the same trial, sponsors can consider stratifying groups at randomization based on key variables such as presence or absence of cirrhosis, baseline HDV RNA level, and genotype/region.

4. Dose Selection

FDA encourages sponsors to use quantitative clinical pharmacology approaches that leverage prior information to optimize dose selection for phase 3 trials. These approaches are addressed in other guidances for industry.[12]

[12] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003) and the draft guidance for industry *Population Pharmacokinetics* (July 2019) (when final, this guidance will represent the FDA's current thinking on this topic).

5. Comparators

See section III.B.1., Trial Design, for a description of potential comparators for use in different trial designs.

6. Efficacy Endpoints

a. Primary endpoints

FDA anticipates that initial approvals for anti-HDV drugs will be based on a surrogate endpoint that is reasonably likely to predict clinical benefit. An appropriate surrogate endpoint for the treatment of HDV should provide evidence of both a decline in virologic replication and an improvement in associated liver inflammation as evident by biochemical response (see section III.B.9., Accelerated Approval (Subpart H) Considerations, for additional information regarding approval under the accelerated approval pathway). For FDA, the following surrogate endpoint could reasonably predict clinical benefit and could be considered to support an accelerated approval:

- The proportion of trial patients with undetectable serum HDV RNA (defined as less than the lower limit of quantification (LLOQ), target not detected (TND)) and ALT normalization.

There are some data suggesting that a 2-$\log_{10}$ decline in HDV RNA is associated with clinical benefit (Farci et al. 2004; Yurdaydin et al. 2019); therefore, in certain situations, such as for drugs that are intended to be used as chronic suppressive therapy, a greater than or equal to 2-$\log_{10}$ decline in HDV RNA and ALT normalization on-treatment could be considered an acceptable surrogate endpoint reasonably likely to predict clinical benefit (see section III.B.9., Accelerated Approval (Subpart H) Considerations). The sponsor can request a Type C formal meeting to discuss the use of a novel surrogate endpoint as the primary basis for drug approval.[13]

The timing of the primary endpoint assessment (whether on-treatment, at the end-of- treatment, or off-treatment after a specified duration of follow-up) will depend on the treatment strategy used (i.e., finite duration of therapy versus chronic suppressive therapy) for a specific drug. FDA encourages the sponsor to discuss its proposed primary efficacy endpoint and the timing of the endpoint assessment with DAVP.

Approval based on a surrogate endpoint reasonably likely to predict clinical benefit will require subsequent confirmation using a clinical endpoint. FDA's preferred clinical endpoint is improvement in clinical outcomes such as decrease in progression to cirrhosis, progression to decompensated liver disease, liver transplantation, hepatocellular carcinoma, and liver-related death. These clinical outcomes should be collected as long-term follow-up data.

[13] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

b. Secondary endpoints

Sponsors should consider the following secondary endpoints:

- Greater than or equal to 2-$\log_{10}$ decline in serum HDV RNA
- HDV RNA less than LLOQ (TND)
- ALT normalization
- Histological response or change in liver stiffness
- Change in Model for End-Stage Liver Disease scores
- Change in Child-Turcotte-Pugh scores

7. Trial Procedures and Timing of Assessments

The optimal timing of the primary endpoint assessment is unknown. Sponsors should consider the following for timing of assessments:

- For therapies intended to be administered indefinitely, an on-treatment assessment after a predefined time period can be acceptable for efficacy.

- For therapies intended to be administered for a finite duration, FDA's preferred endpoint is an off-treatment assessment of efficacy.

8. Statistical Considerations

For recommendations and considerations on statistical analysis methods and issues, see the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) and the article "Statistical Considerations on Subgroup Analysis in Clinical Trials" (Alosh et al. 2015).

a. Efficacy analyses

The preferred primary endpoints for phase 3 trials are described above in section III.B.6., Efficacy Endpoints. Sponsors should consider the following recommendations for analyzing the primary efficacy endpoint:

- The primary analysis should compare the proportion of responders across trial treatment arms. This analysis determines whether effectiveness has been demonstrated.

- The analysis of the primary efficacy endpoint should be performed within important subgroups based on demographic and baseline characteristics (e.g., geographic region, sex, race, age group, screening HDV RNA level, HDV/HBV genotypes, baseline weight and body mass index, baseline ALT, baseline fibrosis/cirrhosis, (if applicable) response to previous treatment regimens). The purpose of these analyses is to explore the consistency of the primary efficacy endpoint result across these subgroups.

b. Noninferiority trials

Because there are no approved therapies for the treatment of chronic HDV infection at this time, a noninferiority trial design is not possible. In the future, should there be approved therapies for the treatment of chronic HDV infection, noninferiority trials may be acceptable. Sponsors should justify proposed noninferiority margins and discuss with DAVP.[14]

c. Combination regimens

Sponsors planning to evaluate a combination regimen of two or more drugs should consult 21 CFR 300.50 regarding combination drugs. Additional recommendations for codevelopment of two new investigational drugs can be found in the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).

9. Accelerated Approval (Subpart H) Considerations

For HDV infection, no surrogate endpoints have been definitively shown to predict clinical benefit. Trials aimed at demonstrating the clinical benefit of an HDV therapy would likely require a prolonged follow-up period. Therefore, FDA anticipates that development programs may opt to pursue accelerated approval pathways based on a surrogate endpoint reasonably likely to predict clinical benefit (see section III.B.6., Efficacy Endpoints). An accelerated approval pathway will require confirmation of clinical benefit through a long-term extension of the original trial or a subsequent additional clinical trial or trials. Sponsors should consider planning for the confirmatory trial(s) during the development of the phase 3 program.

C. Other Considerations

1. Clinical Virology Considerations

Sponsors can find general recommendations for clinical virology assessments in the guidances for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency* and *Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment*. Sponsors should consider the following recommendations specific for HDV infection:

- *Virologic Assessments*

  – For virologic assessments in clinical trials, we recommend the use of FDA-approved or FDA-cleared assays, if available, and a central laboratory. If an investigational assay or assays are used, the sponsor should provide performance characteristics of the assay(s) determined from analytical validation studies using geographically and temporally distinct isolates in addition to detailed descriptions of the methodology. Viral loads should be reported in international units per milliliter (IU/mL).

[14] For additional information on determining noninferiority margins, see the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

- Because HDV requires the HBV envelope protein to propagate, clinical efficacy assessments should include virologic parameters for both HDV and HBV.

- Samples for HDV and HBV quantification, genotypic, and phenotypic analysis should be obtained at multiple time points during treatment and follow-up.

- Where feasible, we recommend determining the genotypes/subtypes of both HDV and HBV present at baseline and, hence, determine if the investigational drug exhibits antiviral activity against all the HDV/HBV genotypes/subtypes represented in the trial.

- *Resistance Assessment*

  - In general, for treatment of HDV infection, virologic failure is defined as a confirmed increase in HDV RNA levels of greater than or equal to 1.0 $\log_{10}$ IU/mL above the nadir value (assuming an initial response of at least 1.0 $\log_{10}$ IU/mL compared with baseline) or having quantifiable HDV RNA after being less than LLOQ (TND). In general, virologic nonresponse is defined as less than or equal to 1.0-$\log_{10}$ IU/mL reduction in HDV RNA levels compared with baseline.

  - Genotypic assessment of resistance should include sequencing of the HDV genome and, for drugs that act through the HBV envelope protein or NTCP receptor, sequencing of the HBsAg coding region where feasible. Any changes, including mixtures, in the amino acid sequence of the target protein (or nucleotide sequence for genome targeting drugs) present in on-treatment or follow-up samples, but not in the baseline sample, can be reported as having developed during therapy.

  - Phenotypic assessment of resistance should include analysis of HDV variants in cell culture, if feasible, and determination of loss of susceptibility to the investigational drug.

  - Before submission of resistance data, contact FDA to obtain the most recent format recommendations for submitting resistance datasets.

  - For drugs with a host target, the frequency of polymorphisms in the target in key U.S. racial groups should be reported and their effect on efficacy assessed in clinical trials.

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