Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs and biologics for the treatment of chronic hepatitis B virus (HBV) infection from the initial investigational new drug application (IND) through the new drug application (NDA)/biologics license application (BLA) and postmarketing phases.[2] This draft guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and the public.[3] Sponsors are also encouraged to communicate with DAVP through the pre-IND consultation program to obtain advice in the development of drugs with unique considerations based on mechanism of action, novel treatment approaches, or the use of novel biomarkers.[4]

This guidance does not address development of vaccines or blood-derived products, as these are regulated by the Center for Biologics Evaluation and Research. This guidance also does not contain discussion of the general issues of statistical analysis or clinical trial design. Those

[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, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the DAVP to discuss specific issues that arise during the development of chronic HBV drugs.

[4] See the DAVP Pre-IND Letter of Instruction web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077776.htm.

topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[5]

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

HBV is an enveloped DNA virus belonging to the *Hepadnavirus* family. The highly stable covalently closed circular viral DNA (cccDNA) functions as a nonreplicative minichromosome and persists throughout the lifespan of infected hepatocytes. The cccDNA is not eliminated by currently available therapies that include drugs from the nucleoside/nucleotide reverse transcriptase inhibitor (NrtIs) class, and pegylated interferon (IFN).

Chronic HBV (CHB) infection results in progressive liver disease ranging from asymptomatic to severe disease with complications including cirrhosis, liver failure, and the development of hepatocellular carcinoma (HCC). In untreated adults with CHB, the cumulative 5-year incidence of cirrhosis is 8 to 20 percent; and among those with cirrhosis, the 5-year cumulative risk of hepatic decompensation is 20 percent, and risk of HCC is 2 to 5 percent (Terrault et al. 2016). An effective vaccine and antiviral therapies are approved for the prevention of HBV infection and treatment of CHB, respectively.

Currently available therapies achieve sustained suppression of HBV DNA while on-treatment with low rates of HBV surface antigen (HBsAg) loss with or without seroconversion to anti-HBsAg (HBsAb). Sustained HBV DNA suppression is associated with serum alanine aminotransferase (ALT) normalization and improvement in liver histology including regression of hepatic fibrosis and cirrhosis (Chang et al. 2010; Marcellin et al. 2013; Buti et al. 2015). Effective HBV therapy reduces disease-related complications such as hepatic decompensation and liver failure, and decreases risk of HCC (Lok et al. 2016; Papatheodoridis et al. 2017). Clearance of HBsAg is associated with reduced risk of hepatic decompensation and improved survival (Terrault et al. 2016). The development of new therapies is targeted at developing treatment regimens of finite duration with low risk of virologic relapse and minimal risk of liver disease progression after the treatment is stopped (Lok et al. 2017).

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

III. DEVELOPMENT PROGRAM

A. General Drug Development Considerations

This section discusses nonclinical and early phase clinical development considerations, followed by issues related to the target population for drug development, assessment of activity in early phase trials, and safety considerations.

1. Early Phase Development Considerations

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

a. Pharmacology/toxicology development considerations

Pharmacology/toxicology development considerations for single HBV drugs should follow the approaches outlined in existing guidances for drug development.[6] Although the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (ICH M3(R2)) recommends nonclinical combination studies to support clinical trials of combination regimens for investigational drugs in early stages of development (referred to in ICH M3(R2) as *early stage entities*), the FDA recommends that for new HBV drug combinations (consisting of two or more early stage investigational drugs), sponsors should discuss with the FDA whether combination toxicology studies should be submitted as part of an IND to support combination clinical trials, including the design of such studies. When combination toxicology studies are conducted, usually no more than two drugs should be tested simultaneously in a particular arm of a toxicology study. Nonclinical combination studies of an investigational drug plus an approved drug or licensed biological product generally are not recommended. Therefore, unless data from nonclinical studies of an investigational drug suggest a potential for serious synergistic toxicity with an approved drug or licensed biological product, combination toxicology studies are not anticipated.

In general, sponsors that have clinical indications for HBV drugs with treatment durations of 6 months or more should conduct carcinogenicity studies.[7] Sponsors developing biological products should follow approaches outlined in the existing ICH guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* and discuss their proposals for a carcinogenicity risk assessment with the FDA during clinical development to facilitate a final assessment needed to support a BLA. Regarding the timing of study submission, sponsors should submit carcinogenicity studies with an initial NDA. Under limited circumstances, the FDA may consider allowing sponsors to initiate carcinogenicity studies (with written agreement) before submitting an NDA and to submit the completed studies during the

[6] See the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*, and *S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.*

[7] See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*.

postmarketing period under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[8]

b. Nonclinical virology development considerations

Sponsors should consider recommendations for general antiviral drug development found in the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency*. However, the development of drugs to treat CHBV infection is rapidly evolving using novel approaches. Therefore, we recommend that sponsors use the pre-IND consultation program to initiate preliminary discussions regarding products and development plans. FDA encourages detailed reports describing the mechanism of action, antiviral activity in cell culture, cytotoxicity and mitochondrial toxicity, animal models, and resistance studies. Additionally, sponsors are advised to provide the following nonclinical virology data for investigational drugs developed specifically for the treatment of CHB.

Resistance and cross-resistance

HBV does not generally grow well enough in cell culture to select for resistant virus. We recommend that resistance assessments be performed for all animal studies that assess the antiviral activity of an investigational drug in infected animals and that a resistance monitoring plan be included in the protocols for all clinical trials that will treat patients with CHB.

- Amino acid substitutions or nucleotide mutations associated with the development of resistance to an investigational drug should be determined by sequencing the drug target and validated by introducing resistance-associated substitutions or mutations into the HBV genome using site-directed mutagenesis, and determining the fold-shift in susceptibility. Results from these studies help identify resistance pathways; and support the drug's proposed mechanism of action. Lack of a shift in susceptibility does not exclude a resistance association for a specific substitution or mutation that occurs in multiple independent events.

Cross resistance should be assessed to determine if resistance against approved HBV drugs confers resistance to the drug being developed and vice versa. The development of cross-resistance to HBV vaccine epitopes should be assessed.

Considerations for antisense oligonucleotides and siRNA investigational drugs

Knockdown of viral protein expression via antisense oligonucleotides and small interfering RNA (siRNA) is an active area for the development of antiviral drugs. These drugs, which have a nucleic acid target, present potential off-target binding at mismatched sequences that could lead to species-specific toxicities not detected in classical toxicity studies. Therefore, we recommend that the following bioinformatics studies be conducted for drugs that use a nucleic acid target. The studies should:

[8] See also the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

- Identify potential off-target matches in the human transcriptome, regardless of tissue expression; for each of these, describe available information on mouse knockouts and human genetic diseases. A plan for monitoring for significant off-target effects should be included in clinical trial protocols.

- Determine the conservation among the investigational off-target human genes with their respective mouse genes that are three or fewer mismatched bases different from the drug to determine if these sites are sufficiently conserved in the mouse such that toxicities related to off-target matches would be present in mice.

- Identify potential off-target matches in the human mitochondrial transcriptome.

- Determine the variation within the off-target matches in the transcriptomes of different populations in the United States to assess whether different populations would be more susceptible to off-target effects than others.

- Determine the effect of different mismatches with respect to off-target effects (i.e., comparing purine to purine versus other mismatches).

Targeting host factors

For drugs targeting host factors, polymorphisms in the gene encoding the target should be assessed to determine if the drug will be more effective or less effective in different populations. If a nonclinical assay to assess the drug effect is available, multiple samples from each of the key racial groups in the United States should be evaluated to determine whether race may be a factor contributing to efficacy. Samples should be collected during clinical trials to determine the virus genotype of patients who respond less favorably to treatment.

c. Clinical pharmacology considerations

In general, dose selection for early efficacy trials should be predicted to provide plasma drug exposures that exceed by several-fold the protein binding-adjusted, cell culture EC_{50} value of the drug for the relevant HBV genotype/subtype. The dose selection should also consider the safety data from the previous phase 1 trials and animal studies.

Sponsors should refer to the appropriate clinical pharmacology guidances for industry to inform the need and design of drug-drug interaction studies and PK studies in patients with renal or hepatic impairment.[9] We encourage sponsors to conduct these studies, if needed, early in

[9] See the guidance for industry *Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*. See also the draft guidances for industry *Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications; In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies*, and *Pharmacokinetics in Patients With Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*. When final, these guidances will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

development to inform the management of drug interactions and the inclusion of patients with renal and hepatic impairment in phase 3 trials as appropriate. See section III.B.6., Dose Selection, for dose selection for phase 2 and 3 trials and section III.C.2., Pharmacokinetic/Pharmacodynamic Considerations, for other PK and pharmacodynamic considerations.

2. Drug Development Population

Therapies should be developed for use in a wide range of patients with CHB including pediatric populations.

Early phase clinical trials should focus on the adult population without cirrhosis. Initial trials can be conducted in treatment-naïve HBV e antigen positive (HBeAg-positive) patients with active disease, or in HBeAg-positive or HBV e antigen negative (HBeAg-negative) patients who are virally suppressed on NrtIs. In addition to endpoints discussed in section III., B., Phase 3 Efficacy Trial Considerations, sponsors can evaluate exploratory endpoints in early phase trials to gather data to inform and support the choice of appropriate endpoints in late phase trials particularly those evaluating treatments of finite durations. Some of these exploratory endpoints may include the following:

- Change in quantitative HBsAg (qHBsAg) concentration at various time points on-treatment
- HBeAg concentration
- HBV RNA
- HBV core-related antigen (HBcrAg)
- cccDNA quantification
- HBsAg fragments
- HBsAg-anti-HBs immune complex

Also depending on the drug's mechanism of action, liver biopsy findings can be used in certain proof-of-concept studies to confirm a novel mode of action and/or to validate surrogate markers of antiviral activity.

CHB is a global disease, and clinical trials are often conducted in multiple countries. Under 21 CFR 312.120, the FDA will accept a well-designed, well-conducted, non-IND foreign study as support for an IND or application for marketing approval if the trial was conducted in accordance with good clinical practice and if the FDA is able to validate the data from the trial through an onsite inspection, if necessary. When sponsors rely on foreign data, these should be supported with information about predominant virus genotypes and subtypes in the region(s). Development programs should include a sufficient number of U.S. patients to ensure applicability of data to the U.S. population. The FDA strongly encourages sponsors to discuss the anticipated number of women and racial representation that will be included in the submission to support an NDA or BLA at the end-of-phase 2 meeting.

3. Safety Considerations

In general, we recommend that initial marketing applications for drugs intended to treat CHB contain a safety database of about 1,000 to 1,500 patients exposed to the proposed dose and duration of treatment. Depending on the drug safety profile and concerns identified during the development process, a larger database or long durations of post-treatment follow-up may be needed.

In addition to routine safety monitoring, specific criteria for monitoring for hepatitis flares or HBV reactivation should be well-defined in the clinical trial protocols. Clinical protocols should include predefined algorithms for data collection in the setting of significant hepatic events to ensure that the relevant data are available for further assessment and adjudication of these cases to differentiate between potential etiologies. The outcomes for all serious hepatic events should be systematically evaluated during clinical development. Evaluation by an independent adjudication committee is encouraged.

For a drug approved for use in patients without cirrhosis or with compensated cirrhosis, the database needed to extend use 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. Similarly, obtaining safety data in other subpopulations, such as in patients coinfected with hepatitis D virus (HDV), may be important for certain clinical development programs. We encourage sponsors to discuss with the FDA safety-related considerations, including but not limited to the size of the safety database, before the initiation of phase 3 trials.

B. Phase 3 Efficacy Trial Considerations

Sponsors can submit an NDA/BLA to support marketing approval of a drug in a single patient population. Such an application should include at least two adequate and well-controlled trials conducted in the proposed population. Alternatively, sponsors can choose to pursue an indication for different populations (e.g., a trial in treatment-naïve patients and a second trial in patients who are virally suppressed on NrtIs). In these situations, the NDA should contain at least one adequate and well-controlled trial in each patient population, with adequate supporting data.

1. Trial Design

Randomized and well-controlled trials are recommended to establish efficacy because of the heterogeneity of the natural course of CHB. Appropriate trial designs depend on whether the therapeutic is intended for chronic suppressive therapy or therapy of finite duration as discussed below.

a. Chronic suppressive therapy

A randomized controlled trial with an approved active control arm with the primary efficacy endpoint of undetectable HBV DNA (defined as less than lower limit of quantification (LLOQ), target not detected (TND)) after 48 weeks on-treatment could be conducted in HBeAg-positive

patients and HBeAg-negative patients. The active comparator should be an antiviral drug that is recommended for treatment of CHB and reflects current practice at the time of trial initiation. The patient population could be treatment-naïve or previously treated patients with detectable HBV DNA.

b. Finite duration therapy

The appropriate trial design depends on the patient population being studied and the treatment regimen being evaluated.

Virally suppressed on NrtIs

To evaluate the primary efficacy outcome of sustained HBV DNA suppression off-treatment with HBsAg loss in patients with active disease (HBeAg-positive or HBeAg-negative CHB) who are virally suppressed on NrtIs, sponsors can consider an add-on superiority trial against placebo with current NrtI treatment regimen as the background therapy. The primary efficacy endpoint of HBsAg loss and sustained HBV DNA suppression should be assessed at the 6-month post-treatment time point with additional follow-up to monitor for durability of response (i.e., sustained HBV DNA suppression and HBsAg loss) off-treatment.

Alternatively, an outcome of sustained HBV DNA suppression off-treatment without HBsAg clearance can be evaluated after a finite treatment duration using a superiority trial design comparing the investigational drug plus an NrtI to an NrtI alone.

Sponsors should use the following criteria for stopping NrtI therapy at the end of the investigational treatment period: (1) applied equally across treatment arms; (2) well-defined in the protocol; and (3) stringent, such as HBsAg loss or substantial HBsAg decline or marked reduction in other important biomarkers identified in phase 2 trials. It is expected that few patients would meet such criteria on the placebo arm. The use of biomarkers as a trigger for treatment interruption should be discussed with the FDA in advance of trial initiation.

Treatment-naïve

An outcome of sustained HBV DNA suppression off-treatment with HBsAg loss can be evaluated to demonstrate superiority to an active control or placebo in treatment-naïve patients in whom a treatment is currently not indicated per treatment guidelines. In certain patient populations (e.g., for patients in the immune-tolerant phase with mild necroinflammation or fibrosis) comparison with placebo may be feasible as current treatment guidelines do not recommend treatment for these patients.

In any of the trial design scenarios, it may be appropriate for patients in the placebo group to be rolled over to active investigational drug before the completion of the trial (e.g., at the prespecified interim analysis). This should be discussed with the FDA before trial enrollment.

Sponsors considering a noninferiority (NI) trial design should discuss in advance their trial designs and justifications of the proposed NI margin based on historical evidence of treatment

effect of the active control. In general, the active comparator in an NI trial should be an FDA-approved drug that is considered the standard of care for the specific indication and population being studied. A detailed protocol and statistical analysis plans (SAPs) should be submitted for review.

2. Trial Population

Patients fulfilling one of the following two criteria for CHB should be enrolled (Centers for Disease Control and Prevention 2012):

(1) Negative immunoglobulin M (IgM) antibodies to HBV core antigen (IgM anti-HBc) AND a positive result on one of the following tests: HBV surface antigen (HBsAg), HBV e antigen (HBeAg), or nucleic acid test for hepatitis B virus DNA (including qualitative, quantitative, and genotype testing); or

(2) Positive HBsAg result or positive nucleic acid test for HBV DNA (including qualitative, quantitative, and genotype testing) or positive HBeAg on two occasions at least 6 months apart (any combination of these tests performed 6 months apart is acceptable).

Sponsors should consider evaluating drug efficacy in key CHB subpopulations, including but not limited to the following:

- HBeAg-positive and HBeAg-negative patients
- Patients with cirrhosis
- Patients with decompensated liver disease

3. Entry Criteria

The presence or absence of cirrhosis at study entry should be documented. The use of a noninvasive modality to define presence or absence of cirrhosis in a trial protocol should be supported by references that summarize performance characteristics and sensitivity and specificity of the modality for identifying patients with cirrhosis. Patients with history of and current evidence of HCC should be excluded.

4. Randomization, Stratification, and Blinding

Sponsors should conduct randomized, double-blind trials whenever feasible to reduce the likelihood of potential biases. In general, trials should be designed to evaluate the effect of investigational therapies in patients with key disease characteristics. If feasible, patient subpopulations should be studied separately. If multiple patient populations are included in the same trial, consideration should be given to stratifying groups at randomization based on variables such as HBeAg status, HBsAg level, presence or absence of cirrhosis, HBV DNA level, treatment history, and HBV genotype; and to ensure adequate number of patients in each stratum to provide informative data.

5. Specific Populations

a. HBV/HIV-1 coinfected patients

The overall treatment goals for HBV/HIV coinfected patients remain identical to those described for the HBV-monoinfected population. The concurrent use of HIV antiretroviral drugs that are also effective against HBV may have implications for treatment cessation with finite duration HBV therapies and possibly confound interpretation of efficacy outcome. Because of the various interactions between HIV and HBV therapies, we recommend sponsors discuss their plans and obtain feedback from the FDA regarding trials in coinfected patients.

b. HBV/HDV coinfected patients

Infection with HDV only occurs in the setting of concurrent HBV infection (Wranke and Wedemeyer 2016). Approximately 15 million people worldwide are living with HBV/HDV coinfection (World Health Organization 2017). Relative to HBV monoinfection, HBV/HDV coinfection leads to more severe liver disease resulting in a greater risk of cirrhosis, HCC, and hepatic decompensation/failure.

The ultimate goal in treating HBV/HDV coinfected patients is clearance or long-term suppression of both viruses. CHB treatment leading to loss of HBsAg may ultimately lead to the clearance of HDV infection (Wranke and Wedemeyer 2016). HDV superinfection frequently leads to spontaneous suppression of HBV (Huang and Lo 2014) and the effect of specific HBV therapies on the interplay between the two viruses cannot be predicted. Recommendations for studies in HBV/HDV coinfection are beyond the scope of this guidance and development plans should be discussed directly with the FDA.

c. Pediatric patients

Pediatric assessments are required under section 505B of the FD&C Act as part of the overall drug development program for a "new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration,"[10] unless those assessments are waived.[11] Sponsors are required to submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting or such other time as may be agreed upon by the FDA and the sponsor.[12]

In the absence of a serious safety signal in adults, sponsors should enroll adolescents concurrently (for the purpose of this guidance, 12 to younger than 18 years of age) with adults in phase 3 trials and make every effort to obtain confirmatory PK and safety data from a cohort in this age group as part of the data included at the time of filing of the original NDA/BLA.[13]

[10] See section 505B(a)(1)(A) of the FD&C Act; 21 U.S.C. 355c(a)(1)(A).

[11] See section 505B(a)(5) of the FD&C Act.

[12] See section 505B(e)(2)(A)(ii) of the FD&C Act; see also the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

Because progressive liver disease is uncommon in young children with HBV infection, it is generally not recommended to include patients younger than 2 years in most development programs. Further, treatment generally is not recommended in children younger than 2 years of age as per current treatment guidelines (Terrault et al. 2016). Sponsors should discuss their plans for pediatric assessments with the review division and be aware of timing and content requirements for pediatric study plans under section 505B(e) of the FD&C Act.

In general, pediatric clinical trials can be initiated after phase 2 adult data characterizing the safety profile and preliminary evidence of efficacy are available. Typically, the non-adolescent pediatric population (for the purpose of this guidance, 2 to younger than 12 years of age) is divided into several groups or cohorts according to age or weight for enrollment into trials. Weight, rather than age, is the preferred criterion for enrollment because dosing recommendations for most antiviral drugs are weight-based. In addition, within clinical studies, sponsors should enroll the cohorts in parallel rather than in series, unless a drug has a specific safety or drug disposition factor that warrants a different approach.

Sponsors should discuss with the FDA initial pediatric PK data and results of available modeling and simulation before dose selection for pediatric treatment trials. Partial pediatric extrapolation of efficacy may be acceptable for HBV drugs because antiviral effects are sufficiently similar between adult and pediatric populations. Therefore, after critical PK parameters for a drug are identified from adult data, pediatric development programs can rely on matching the relevant pediatric and adult exposure parameters to demonstrate effectiveness in pediatric populations in which treatment is indicated as per current treatment guidelines. Additional data should be obtained to assess whether antiviral activity is comparable to that observed in adult trials.

The pediatric trials should also obtain data to support safety in pediatric populations; in general, a safety database of about 100 patients receiving the proposed dose for at least 48 weeks or prespecified duration for drug with finite treatment duration, and adequately distributed across the pediatric population for which studies are required and not waived or deferred. If clinical trials in adults have demonstrated differences in safety profile or dosing based on fibrosis stage, pediatric patients should be assessed for presence or absence of cirrhosis using the most appropriate modality for each study location.

Section 505B of the FD&C Act also mandates that the requisite pediatric assessments be conducted using a formulation of the drug that is appropriate for each pediatric group being studied.[14] Adult formulations generally are considered appropriate for adolescent patients (approximately 12 to 18 years of age) (Momper et al. 2013), but younger patients, who may not be able to swallow pills, may require different formulations. Therefore, pediatric formulation development should begin as early as possible to enable the development of appropriate pediatric formulations of investigational drugs.

[13] We note that, for applications to which section 505B applies, all pediatric assessments must be submitted with the application unless those assessments have been deferred (section 505B(a)(1)(A)).

[14] See section 505B(a)(2)A) of the FD&C Act.

6. Dose Selection

Sponsors are encouraged to use quantitative clinical pharmacology approaches that leverage prior information to inform dose selection for phase 2 trials and optimize dose selection for phase 3 trials. The results from the proof-of-concept antiviral activity trials should be used to guide selection of doses to be evaluated in phase 2 dose ranging trials with a consideration to avoid the risk of the development of resistant virus and potential concerns of treatment failure caused by subtherapeutic exposure. To optimize the selected dose for phase 3 trials, quantitative clinical pharmacology approaches can be used to predict HBV DNA reduction in the planned trials. Exposure-safety analyses, based on events with plausible causality to the drug and with clinical relevance, should also be evaluated.

7. Efficacy Endpoints

New therapies could be evaluated in clinical trials using any of the following efficacy endpoints:

- Suppression of HBV DNA (defined as less than LLOQ, TND) on-treatment — similar to currently available chronic NrtI therapies

- Sustained suppression (more than 6 months) of HBV DNA (less than LLOQ, TND) off-treatment after a finite duration of therapy

- Sustained suppression (more than 6 months) of HBV DNA (less than LLOQ, TND) off-treatment with HBsAg loss (less than 0.05 international unit/milliliter (IU/mL)) with or without HBsAb seroconversion after a finite duration of therapy

At present, utility of reduction in HBsAg from baseline (without complete clearance) for assessing response to CHB therapies is unclear because of inconsistent correlations between qHBsAg and clinical response (Hu et al. 2018; Thompson et al. 2010; Chan et al. 2011).

A limited number of secondary endpoint(s) (e.g., HBeAg loss, anti-HBe seroconversion in HBeAg positive patients, ALT normalization) should be considered for testing using appropriate statistical methods for multiplicity. Biochemical serum markers such as ALT values vary between laboratories, and lack of normalization of ALT may often be confounded by presence of other chronic liver diseases such as nonalcoholic fatty liver disease.

Other important endpoints: Assessing progression of liver disease

Except for patients with advanced or decompensated cirrhosis, a statistically rigorous evaluation of endpoints of liver progression can be challenging because these events occur infrequently until late in the course of CHB. However, treatment effects on these endpoints provide useful clinical information, and trials evaluating them could be used to support an expanded indication or patient population and could be summarized in appropriate sections of the label.
Some of the parameters or clinical outcomes that sponsors can consider include the following:

- Change in Model for End Stage Liver Disease scores

- Change in Child-Turcotte-Pugh scores
- Progression to liver failure requiring transplantation or resulting in death
- Occurrence of HCC

Treatment-related regression of fibrosis or cirrhosis, as assessed by liver biopsy or noninvasive methods, can also be appropriate for display in the label and should be discussed with the division when protocols evaluating these endpoints are being designed.

8. Trial Procedures and Timing of Assessments

Biochemical, serological, virological, and histological endpoints can be used to assess the effectiveness of therapy. For drugs with finite treatment durations, the optimal time point to assess the primary efficacy endpoint of sustained virologic response is 6 months or longer after cessation of therapy. Additionally, the most appropriate time point to assess efficacy endpoints depend on the mechanism of action and half-life of the drug. Longer term follow-up may be useful to confirm durability of treatment response and to measure clinical outcomes.

9. Statistical Considerations

In general, a detailed protocol and SAP stating the trial hypotheses, analysis methods, and all other relevant details should be provided to DAVP before trial initiation. For statistical analysis methods and issues, see the FDA guidances for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* and *Non-Inferiority Clinical Trials to Establish Effectiveness* and the FDA White Paper Statistical Considerations on Subgroup Analysis in Clinical Trials (Alosh et al. 2015).

a. Analysis populations

All patients who are randomized and received at least one dose of assigned therapy during the trial should be included in the primary efficacy analysis. Any possibility of randomized patients who do not receive treatment in either or both arms should be minimized.

b. Efficacy analyses

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

For subgroup analyses, the analysis of the primary efficacy endpoint should be performed within important demographic and baseline characteristics (e.g., geographic region, sex, race, age group, HBV genotype, HBeAg status, screening HBV DNA, baseline weight, and body mass index, baseline ALT, baseline fibrosis/cirrhosis, and (if applicable) prior response to previous treatment regimens). The purpose of these analyses is to explore the consistency of the primary efficacy endpoint result across these subgroups.

Treatment-by-region interaction should be investigated and reported to assess consistency of the efficacy results. Treatment-by-HBeAg status interaction should also be investigated if HBeAg-positive and -negative patients are enrolled in the trial.

c. Handling of missing data

Sponsors should make every attempt to limit discontinuation of patients from the trial. When the loss is unavoidable, sponsors should explain the causes of missing data and attempt to determine the final status of a patient who does not complete the protocol. Analyses excluding patients with missing data or other post-treatment outcomes can be biased because patients who do not complete the trial may differ substantially in both measured and unmeasured ways compared to patients who remain in the trial. The primary method of handling missing data in the analysis should be prespecified in the protocol or the SAP. Sensitivity analyses should demonstrate that the primary analysis results are robust to the assumptions regarding missing data.

10. Accelerated Approval (Subpart H) Considerations

For CHB, HBV DNA suppression with or without HBsAg loss is considered a validated surrogate endpoint that has been demonstrated to predict clinical outcomes; and this endpoint could be used to support a traditional approval. Sponsors should discuss plans to use any surrogate endpoints that are reasonably likely to predict clinical benefit to support accelerated approval with the FDA.[15] After accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit.[16]

11. Benefit-Risk Considerations

A thorough and comprehensive benefit-risk assessment ensures that the benefits outweigh potential risks to the intended population. Benefit-risk assessment takes into consideration demonstrated therapeutic effect of the new drug, and observed safety profile in the context of underlying disease and current treatment options available for the indication.

C. Other Considerations

1. Clinical Virology Considerations

Samples for HBV quantification, genotypic, and phenotypic analysis should be obtained at different time points during treatment and follow-up. Timing of sample collection should be based on initial observations of potency, and on-treatment and off-treatment durability. The genotypes and phenotypes of baseline and virologic failure isolates should be determined (virologic failure defined as a confirmed increase of greater than or equal to 1 $\log_{10}$ HBV DNA copies/mL above nadir, quantifiable HBV DNA after being less than LLOQ, or never achieved HBV DNA levels less than LLOQ). Genotypes of baseline and on-therapy virologic failure

[15] See section 506(c) of the FD&C Act; 21 CFR part 314, subpart H; 21 CFR part 601, subpart E.

[16] See 21 CFR 314.510; 21 CFR 601.41.

isolates should be compared and newly emerged drug resistance-associated substitutions/mutations should be identified. HBV DNA from patients with genotypic resistance to the investigational drug should be cloned in an HBV genome background and susceptibility to the investigational drug should be determined.

- There are 10 recognized HBV genotypes (genotypes A through H) as well as subtypes identified for genotypes A through F. The different HBV genotypes/subtypes encode distinct viral proteins and may exhibit differential responses to an investigational drug, which could confound efficacy results in clinical trials if the drug is only effective against some genotype/subtypes. Therefore, we recommend determining the genotypes/subtypes of HBV infection present at baseline to determine if the investigational drug exhibits antiviral activity against all HBV genotypes/subtypes. The assay, with performance characteristics, used to genotype the HBV samples in enrolled patients should be included with the clinical trial protocol. It may be important to confirm the genotype/subtype by phylogenetic analysis.

- For resistance analyses, any changes, including mixtures, in the amino acid sequence of the target protein, or DNA 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. In addition, baseline samples should be analyzed to identify HBV genetic polymorphisms that are associated with differential antiviral activity against the investigational drug. Sponsors should consult the FDA early for the most current format for submission of resistance data and if Next Generation Sequencing (NGS) will be used.

- There is a risk of the development of resistance against an antiviral drug that targets similar viral proteins in different virus species in patients coinfected with HIV and HBV. Because of this risk, we recommend assessing for the development of resistance and cross-resistance in the viral proteins of both HIV-1 and HBV when appropriate.

- For all virologic assessments in clinical trials, we recommend the use of FDA-approved or FDA-cleared assays, when available, and a central laboratory. Sponsors can collect results from local lab tests, identifying the assay(s) used. If investigational assay(s) are used, performance characteristics <u>of the assay(s) determined from analytical validation studies using</u> geographically and temporally distinct isolates should be provided in addition to detailed descriptions of the methodology.[17] Drugs that require assays to identify the infected population benefiting from treatment (e.g., specific genotypes or resistant populations) may require a companion diagnostic. Additional recommendations can be found in the draft guidance for industry and FDA staff *Principles for Codevelopment of an In Vitro Companion Diagnostic Device With a Therapeutic Product*.[18]

[17] See the IDE (Investigational Device Exemption) web page available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm.

[18] When final, this guidance will represent the FDA's current thinking on this topic.

- Sponsors are encouraged to submit a resistance monitoring plan early in development. If resistance evaluation in clinical trials involves NGS, we recommend that sponsors discuss details of the NGS approach with the FDA. Submission of NGS data in fastq format is strongly encouraged.

- HBV should be genotyped for any instances where HBV DNA is detected in long-term follow-up to distinguish relapse from reinfection.

2. Pharmacokinetic/Pharmacodynamic Considerations

Trials conducted in HBV-infected patients should include assessment of pharmacokinetics and the relationship between drug exposure (e.g., minimum or maximum plasma concentration (C_{min} or C_{max}), area under the curve) and virologic success and toxicity in all patients.

Sponsors can use a combination of intensive and sparse sampling throughout development to characterize the pharmacokinetics of the investigational drug. For example, sponsors should implement an intensive sampling schedule in early phase monotherapy trials. In longer term trials, an intensive sampling schedule might not be feasible. Alternatively, sponsors can combine sparse sampling from these trials with intensive PK data from earlier trials for population PK analysis. Sponsors should obtain multiple sparse PK samples from as many patients as possible including at the time of key virologic assessments. It is important to document dosing times and plasma sampling times.

Sponsors can use the following two broad approaches to characterize the relationship between drug exposure and viral kinetics or virologic suppression of the investigational drug, depending on the development stage and purpose of the analysis. Both approaches allow for exploration of relevant covariates.

(1) To aid the design of phase 2b or phase 3 trials, with respect to selection of the dosage regimen, a mechanistic approach relating drug concentrations and viral kinetics should be considered. A mechanistic modeling approach should also account for the development of resistance to the investigational drug and the intended patient population. For combination therapy, the potential of additive or synergistic antiviral effects can be incorporated in the model to assist optimization of the dose combination.

(2) A simplified analysis relating the proportion of patients with virologic suppression or virologic failure and appropriate exposure variable (e.g., minimum concentration or area under the plasma drug concentration versus time curve) can be used to support evidence of activity and to support dose selection.

Exposure-response safety analyses should consider the mechanistic on-target and off-target effects of the investigational drug and adverse events that are more frequent in the investigational drug arm. The appropriate exposure parameter and modeling approach depends on the investigational drug and toxicity.

673 *3. Labeling Considerations*
674
675 Severe acute exacerbations of HBV infection may occur after discontinuation of anti-HBV
676 therapy. Hepatic function should be monitored closely with both clinical and laboratory follow-
677 up for at least several months in patients who discontinue anti-HBV therapy. In certain
678 circumstances, resumption of anti-HBV therapy may be warranted. These concerns should be
679 adequately conveyed in drug labeling.
680
681 Development of HIV-1 resistance against anti-HBV drugs with activity against HIV-1 is a
682 potential risk that should be conveyed in labeling.
683

GLOSSARY OF ACRONYMS

ALT	alanine aminotransferase
CC_{50}	concentration inhibiting 50 percent cell growth
cccDNA	covalently closed circular DNA
CHB	chronic hepatitis B
$EC_{50/90}$	effective drug concentration inhibiting 50 or 90 percent virus replication
FD&C Act	Federal Food, Drug, and Cosmetic Act
HBeAg	HBV enigma antigen
HBsAb	antibody specific to HBsAg
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HBV DNA	hepatitis B virus DNA
HCC	hepatocellular carcinoma
HDV	hepatitis delta virus
HIV	human immunodeficiency virus
IFN	interferon
IgM	immunoglobulin M
IU	international unit
LLOQ	lower limit of quantification
mL	milliliter
NrtI	nucleoside/nucleotide reverse transcriptase inhibitor
NGS	Next Generation Sequencing
NI	noninferiority
PHH	primary human hepatocyte
PK	pharmacokinetic
qHBsAg	quantitative HBsAg
RNA	ribonucleic acid
rt	reverse transcriptase
SAP	statistical analysis plan
TND	target not detected
WHV	woodchuck hepatitis virus

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