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# **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## ***DRAFT GUIDANCE***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  
Center for Drug Evaluation and Research (CDER)**

**November 2018  
Clinical/Antimicrobial**

# **Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment Guidance for Industry**

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## **Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment Guidance for Industry<sup>1</sup>**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

### **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.<sup>2</sup> This draft guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and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.<sup>3</sup> 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.<sup>4</sup>

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

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<sup>1</sup> 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.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

<sup>3</sup> 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.

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

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32 topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical*  
33 *Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.<sup>5</sup>  
34

35 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
36 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
37 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
38 the word *should* in Agency guidances means that something is suggested or recommended, but  
39 not required.  
40

## 41 **II. BACKGROUND**

42  
43  
44 HBV is an enveloped DNA virus belonging to the *Hepadnavirus* family. The highly stable  
45 covalently closed circular viral DNA (cccDNA) functions as a nonreplicative minichromosome  
46 and persists throughout the lifespan of infected hepatocytes. The cccDNA is not eliminated by  
47 currently available therapies that include drugs from the nucleoside/nucleotide reverse  
48 transcriptase inhibitor (NrtIs) class, and pegylated interferon (IFN).  
49

50 Chronic HBV (CHB) infection results in progressive liver disease ranging from asymptomatic to  
51 severe disease with complications including cirrhosis, liver failure, and the development of  
52 hepatocellular carcinoma (HCC). In untreated adults with CHB, the cumulative 5-year incidence  
53 of cirrhosis is 8 to 20 percent; and among those with cirrhosis, the 5-year cumulative risk of  
54 hepatic decompensation is 20 percent, and risk of HCC is 2 to 5 percent (Terrault et al. 2016).  
55 An effective vaccine and antiviral therapies are approved for the prevention of HBV infection  
56 and treatment of CHB, respectively.  
57

58 Currently available therapies achieve sustained suppression of HBV DNA while on-treatment  
59 with low rates of HBV surface antigen (HBsAg) loss with or without seroconversion to anti-  
60 HBsAg (HBsAb). Sustained HBV DNA suppression is associated with serum alanine  
61 aminotransferase (ALT) normalization and improvement in liver histology including regression  
62 of hepatic fibrosis and cirrhosis (Chang et al. 2010; Marcellin et al. 2013; Buti et al. 2015).  
63 Effective HBV therapy reduces disease-related complications such as hepatic decompensation  
64 and liver failure, and decreases risk of HCC (Lok et al. 2016; Papatheodoridis et al. 2017).  
65 Clearance of HBsAg is associated with reduced risk of hepatic decompensation and improved  
66 survival (Terrault et al. 2016). The development of new therapies is targeted at developing  
67 treatment regimens of finite duration with low risk of virologic relapse and minimal risk of liver  
68 disease progression after the treatment is stopped (Lok et al. 2017).  
69  
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<sup>5</sup> 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>.

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71 **III. DEVELOPMENT PROGRAM**

72

73 **A. General Drug Development Considerations**

74

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

78

79 **1. Early Phase Development Considerations**

80

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

83

84 **a. Pharmacology/toxicology development considerations**

85

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

101

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

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<sup>6</sup> 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*.

<sup>7</sup> See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*.

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111 postmarketing period under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act  
112 (FD&C Act).<sup>8</sup>

113

114 b. Nonclinical virology development considerations

115

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

125

### **Resistance and cross-resistance**

126

127  
128 HBV does not generally grow well enough in cell culture to select for resistant virus. We  
129 recommend that resistance assessments be performed for all animal studies that assess the  
130 antiviral activity of an investigational drug in infected animals and that a resistance monitoring  
131 plan be included in the protocols for all clinical trials that will treat patients with CHB.

132

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

141

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

145

### **Considerations for antisense oligonucleotides and siRNA investigational drugs**

146

147  
148 Knockdown of viral protein expression via antisense oligonucleotides and small interfering RNA  
149 (siRNA) is an active area for the development of antiviral drugs. These drugs, which have a  
150 nucleic acid target, present potential off-target binding at mismatched sequences that could lead  
151 to species-specific toxicities not detected in classical toxicity studies. Therefore, we recommend  
152 that the following bioinformatics studies be conducted for drugs that use a nucleic acid target.  
153 The studies should:

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<sup>8</sup> 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*.

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- 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**

174

175

176 For drugs targeting host factors, polymorphisms in the gene encoding the target should be

177 assessed to determine if the drug will be more effective or less effective in different populations.

178 If a nonclinical assay to assess the drug effect is available, multiple samples from each of the key

179 racial groups in the United States should be evaluated to determine whether race may be a factor

180 contributing to efficacy. Samples should be collected during clinical trials to determine the virus

181 genotype of patients who respond less favorably to treatment.

#### **c. Clinical pharmacology considerations**

182

183

184

185 In general, dose selection for early efficacy trials should be predicted to provide plasma drug

186 exposures that exceed by several-fold the protein binding-adjusted, cell culture EC<sub>50</sub> value of the

187 drug for the relevant HBV genotype/subtype. The dose selection should also consider the safety

188 data from the previous phase 1 trials and animal studies.

189

190 Sponsors should refer to the appropriate clinical pharmacology guidances for industry to inform

191 the need and design of drug-drug interaction studies and PK studies in patients with renal or

192 hepatic impairment.<sup>9</sup> We encourage sponsors to conduct these studies, if needed, early in

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<sup>9</sup> 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>.



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

198

### 199 2. *Drug Development Population*

200

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

203

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

212

- 213 • Change in quantitative HBsAg (qHBsAg) concentration at various time points on-  
214 treatment
- 215 • HBeAg concentration
- 216 • HBV RNA
- 217 • HBV core-related antigen (HBcrAg)
- 218 • cccDNA quantification
- 219 • HBsAg fragments
- 220 • HBsAg-anti-HBs immune complex

221

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

225

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

236

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### 237 3. *Safety Considerations*

238  
239 In general, we recommend that initial marketing applications for drugs intended to treat CHB  
240 contain a safety database of about 1,000 to 1,500 patients exposed to the proposed dose and  
241 duration of treatment. Depending on the drug safety profile and concerns identified during the  
242 development process, a larger database or long durations of post-treatment follow-up may be  
243 needed.

244  
245 In addition to routine safety monitoring, specific criteria for monitoring for hepatitis flares or  
246 HBV reactivation should be well-defined in the clinical trial protocols. Clinical protocols should  
247 include predefined algorithms for data collection in the setting of significant hepatic events to  
248 ensure that the relevant data are available for further assessment and adjudication of these cases  
249 to differentiate between potential etiologies. The outcomes for all serious hepatic events should  
250 be systematically evaluated during clinical development. Evaluation by an independent  
251 adjudication committee is encouraged.

252  
253 For a drug approved for use in patients without cirrhosis or with compensated cirrhosis, the  
254 database needed to extend use to the decompensated cirrhotic population would depend on the  
255 safety profile of the investigational drug and the overall benefit-risk profile for the indicated  
256 population. Similarly, obtaining safety data in other subpopulations, such as in patients  
257 coinfecting with hepatitis D virus (HDV), may be important for certain clinical development  
258 programs. We encourage sponsors to discuss with the FDA safety-related considerations,  
259 including but not limited to the size of the safety database, before the initiation of phase 3 trials.

### 260 **B. Phase 3 Efficacy Trial Considerations**

261  
262 Sponsors can submit an NDA/BLA to support marketing approval of a drug in a single patient  
263 population. Such an application should include at least two adequate and well-controlled trials  
264 conducted in the proposed population. Alternatively, sponsors can choose to pursue an  
265 indication for different populations (e.g., a trial in treatment-naïve patients and a second trial in  
266 patients who are virally suppressed on NrtIs). In these situations, the NDA should contain at  
267 least one adequate and well-controlled trial in each patient population, with adequate supporting  
268 data.

#### 269 270 271 1. *Trial Design*

272  
273 Randomized and well-controlled trials are recommended to establish efficacy because of the  
274 heterogeneity of the natural course of CHB. Appropriate trial designs depend on whether the  
275 therapeutic is intended for chronic suppressive therapy or therapy of finite duration as discussed  
276 below.

##### 277 278 a. Chronic suppressive therapy

279  
280 A randomized controlled trial with an approved active control arm with the primary efficacy  
281 endpoint of undetectable HBV DNA (defined as less than lower limit of quantification (LLOQ),  
282 target not detected (TND)) after 48 weeks on-treatment could be conducted in HBeAg-positive

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

287  
288           b.       Finite duration therapy

289  
290 The appropriate trial design depends on the patient population being studied and the treatment  
291 regimen being evaluated.

### **Virally suppressed on NrtIs**

292  
293  
294  
295 To evaluate the primary efficacy outcome of sustained HBV DNA suppression off-treatment  
296 with HBsAg loss in patients with active disease (HBeAg-positive or HBeAg-negative CHB) who  
297 are virally suppressed on NrtIs, sponsors can consider an add-on superiority trial against placebo  
298 with current NrtI treatment regimen as the background therapy. The primary efficacy endpoint  
299 of HBsAg loss and sustained HBV DNA suppression should be assessed at the 6-month post-  
300 treatment time point with additional follow-up to monitor for durability of response (i.e.,  
301 sustained HBV DNA suppression and HBsAg loss) off-treatment.

302  
303 Alternatively, an outcome of sustained HBV DNA suppression off-treatment without HBsAg  
304 clearance can be evaluated after a finite treatment duration using a superiority trial design  
305 comparing the investigational drug plus an NrtI to an NrtI alone.

306  
307 Sponsors should use the following criteria for stopping NrtI therapy at the end of the  
308 investigational treatment period: (1) applied equally across treatment arms; (2) well-defined in  
309 the protocol; and (3) stringent, such as HBsAg loss or substantial HBsAg decline or marked  
310 reduction in other important biomarkers identified in phase 2 trials. It is expected that few  
311 patients would meet such criteria on the placebo arm. The use of biomarkers as a trigger for  
312 treatment interruption should be discussed with the FDA in advance of trial initiation.

### **Treatment-naïve**

313  
314  
315  
316 An outcome of sustained HBV DNA suppression off-treatment with HBsAg loss can be  
317 evaluated to demonstrate superiority to an active control or placebo in treatment-naïve patients in  
318 whom a treatment is currently not indicated per treatment guidelines. In certain patient  
319 populations (e.g., for patients in the immune-tolerant phase with mild necroinflammation or  
320 fibrosis) comparison with placebo may be feasible as current treatment guidelines do not  
321 recommend treatment for these patients.

322  
323 In any of the trial design scenarios, it may be appropriate for patients in the placebo group to be  
324 rolled over to active investigational drug before the completion of the trial (e.g., at the  
325 prespecified interim analysis). This should be discussed with the FDA before trial enrollment.

326  
327 Sponsors considering a noninferiority (NI) trial design should discuss in advance their trial  
328 designs and justifications of the proposed NI margin based on historical evidence of treatment

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

333

#### 334 2. *Trial Population*

335

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

338

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

343

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

347

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

350

- 351 • HBeAg-positive and HBeAg-negative patients
- 352 • Patients with cirrhosis
- 353 • Patients with decompensated liver disease

354

#### 355 3. *Entry Criteria*

356

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

362

#### 363 4. *Randomization, Stratification, and Blinding*

364

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

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374 5. *Specific Populations*

375

376 a. HBV/HIV-1 coinfecting patients

377

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

384

385 b. HBV/HDV coinfecting patients

386

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

392

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

400

401 c. Pediatric patients

402

403 Pediatric assessments are required under section 505B of the FD&C Act as part of the overall  
404 drug development program for a “new active ingredient, new indication, new dosage form, new  
405 dosing regimen, or new route of administration,”<sup>10</sup> unless those assessments are waived.<sup>11</sup>  
406 Sponsors are required to submit pediatric study plans no later than 60 days after an end-of-phase  
407 2 meeting or such other time as may be agreed upon by the FDA and the sponsor.<sup>12</sup>

408

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

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<sup>10</sup> See section 505B(a)(1)(A) of the FD&C Act; 21 U.S.C. 355c(a)(1)(A).

<sup>11</sup> See section 505B(a)(5) of the FD&C Act.

<sup>12</sup> 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.

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

419  
420 In general, pediatric clinical trials can be initiated after phase 2 adult data characterizing the  
421 safety profile and preliminary evidence of efficacy are available. Typically, the non-adolescent  
422 pediatric population (for the purpose of this guidance, 2 to younger than 12 years of age) is  
423 divided into several groups or cohorts according to age or weight for enrollment into trials.  
424 Weight, rather than age, is the preferred criterion for enrollment because dosing  
425 recommendations for most antiviral drugs are weight-based. In addition, within clinical studies,  
426 sponsors should enroll the cohorts in parallel rather than in series, unless a drug has a specific  
427 safety or drug disposition factor that warrants a different approach.

428  
429 Sponsors should discuss with the FDA initial pediatric PK data and results of available modeling  
430 and simulation before dose selection for pediatric treatment trials. Partial pediatric extrapolation  
431 of efficacy may be acceptable for HBV drugs because antiviral effects are sufficiently similar  
432 between adult and pediatric populations. Therefore, after critical PK parameters for a drug are  
433 identified from adult data, pediatric development programs can rely on matching the relevant  
434 pediatric and adult exposure parameters to demonstrate effectiveness in pediatric populations in  
435 which treatment is indicated as per current treatment guidelines. Additional data should be  
436 obtained to assess whether antiviral activity is comparable to that observed in adult trials.

437  
438 The pediatric trials should also obtain data to support safety in pediatric populations; in general,  
439 a safety database of about 100 patients receiving the proposed dose for at least 48 weeks or  
440 prespecified duration for drug with finite treatment duration, and adequately distributed across  
441 the pediatric population for which studies are required and not waived or deferred. If clinical  
442 trials in adults have demonstrated differences in safety profile or dosing based on fibrosis stage,  
443 pediatric patients should be assessed for presence or absence of cirrhosis using the most  
444 appropriate modality for each study location.

445  
446 Section 505B of the FD&C Act also mandates that the requisite pediatric assessments be  
447 conducted using a formulation of the drug that is appropriate for each pediatric group being  
448 studied.<sup>14</sup> Adult formulations generally are considered appropriate for adolescent patients  
449 (approximately 12 to 18 years of age) (Momper et al. 2013), but younger patients, who may not  
450 be able to swallow pills, may require different formulations. Therefore, pediatric formulation  
451 development should begin as early as possible to enable the development of appropriate pediatric  
452 formulations of investigational drugs.

453

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<sup>13</sup> 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)).

<sup>14</sup> See section 505B(a)(2)(A) of the FD&C Act.

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454           6.     *Dose Selection*

455  
456 Sponsors are encouraged to use quantitative clinical pharmacology approaches that leverage  
457 prior information to inform dose selection for phase 2 trials and optimize dose selection for  
458 phase 3 trials. The results from the proof-of-concept antiviral activity trials should be used to  
459 guide selection of doses to be evaluated in phase 2 dose ranging trials with a consideration to  
460 avoid the risk of the development of resistant virus and potential concerns of treatment failure  
461 caused by subtherapeutic exposure. To optimize the selected dose for phase 3 trials, quantitative  
462 clinical pharmacology approaches can be used to predict HBV DNA reduction in the planned  
463 trials. Exposure-safety analyses, based on events with plausible causality to the drug and with  
464 clinical relevance, should also be evaluated.

465  
466           7.     *Efficacy Endpoints*

467  
468 New therapies could be evaluated in clinical trials using any of the following efficacy endpoints:

- 469
- 470       • Suppression of HBV DNA (defined as less than LLOQ, TND) on-treatment — similar to
  - 471       currently available chronic NrtI therapies
  - 472
  - 473       • Sustained suppression (more than 6 months) of HBV DNA (less than LLOQ, TND) off-
  - 474       treatment after a finite duration of therapy
  - 475
  - 476       • Sustained suppression (more than 6 months) of HBV DNA (less than LLOQ, TND) off-
  - 477       treatment with HBsAg loss (less than 0.05 international unit/milliliter (IU/mL)) with or
  - 478       without HBsAb seroconversion after a finite duration of therapy
  - 479

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

483  
484 A limited number of secondary endpoint(s) (e.g., HBeAg loss, anti-HBe seroconversion in  
485 HBeAg positive patients, ALT normalization) should be considered for testing using appropriate  
486 statistical methods for multiplicity. Biochemical serum markers such as ALT values vary  
487 between laboratories, and lack of normalization of ALT may often be confounded by presence of  
488 other chronic liver diseases such as nonalcoholic fatty liver disease.

489  
490 **Other important endpoints: Assessing progression of liver disease**

491  
492 Except for patients with advanced or decompensated cirrhosis, a statistically rigorous evaluation  
493 of endpoints of liver progression can be challenging because these events occur infrequently  
494 until late in the course of CHB. However, treatment effects on these endpoints provide useful  
495 clinical information, and trials evaluating them could be used to support an expanded indication  
496 or patient population and could be summarized in appropriate sections of the label.

497 Some of the parameters or clinical outcomes that sponsors can consider include the following:

- 498
- 499       • Change in Model for End Stage Liver Disease scores

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

503  
504 Treatment-related regression of fibrosis or cirrhosis, as assessed by liver biopsy or noninvasive  
505 methods, can also be appropriate for display in the label and should be discussed with the  
506 division when protocols evaluating these endpoints are being designed.

### 507 508 8. *Trial Procedures and Timing of Assessments*

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

### 515 516 517 9. *Statistical Considerations*

518  
519 In general, a detailed protocol and SAP stating the trial hypotheses, analysis methods, and all  
520 other relevant details should be provided to DAVP before trial initiation. For statistical analysis  
521 methods and issues, see the FDA guidances for industry *Providing Clinical Evidence of*  
522 *Effectiveness for Human Drug and Biological Products* and *Non-Inferiority Clinical Trials to*  
523 *Establish Effectiveness* and the FDA White Paper *Statistical Considerations on Subgroup*  
524 *Analysis in Clinical Trials* (Alosh et al. 2015).

#### 525 526 a. Analysis populations

527  
528 All patients who are randomized and received at least one dose of assigned therapy during the  
529 trial should be included in the primary efficacy analysis. Any possibility of randomized patients  
530 who do not receive treatment in either or both arms should be minimized.

#### 531 532 b. Efficacy analyses

533  
534 The primary analysis should compare the proportion of responders across trial treatment arms.  
535 This analysis determines whether effectiveness has been demonstrated.

536  
537 For subgroup analyses, the analysis of the primary efficacy endpoint should be performed within  
538 important demographic and baseline characteristics (e.g., geographic region, sex, race, age  
539 group, HBV genotype, HBeAg status, screening HBV DNA, baseline weight, and body mass  
540 index, baseline ALT, baseline fibrosis/cirrhosis, and (if applicable) prior response to previous  
541 treatment regimens). The purpose of these analyses is to explore the consistency of the primary  
542 efficacy endpoint result across these subgroups.

543



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

547

548 c. Handling of missing data

549

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

558

559 10. *Accelerated Approval (Subpart H) Considerations*

560

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

568

569 11. *Benefit-Risk Considerations*

570

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

575

576 C. **Other Considerations**

577

578 1. *Clinical Virology Considerations*

579

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

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

<sup>16</sup> See 21 CFR 314.510; 21 CFR 601.41.

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

- 591
- 592 • There are 10 recognized HBV genotypes (genotypes A through H) as well as subtypes  
593 identified for genotypes A through F. The different HBV genotypes/subtypes encode  
594 distinct viral proteins and may exhibit differential responses to an investigational drug,  
595 which could confound efficacy results in clinical trials if the drug is only effective against  
596 some genotype/subtypes. Therefore, we recommend determining the genotypes/subtypes  
597 of HBV infection present at baseline to determine if the investigational drug exhibits  
598 antiviral activity against all HBV genotypes/subtypes. The assay, with performance  
599 characteristics, used to genotype the HBV samples in enrolled patients should be  
600 included with the clinical trial protocol. It may be important to confirm the  
601 genotype/subtype by phylogenetic analysis.  
602
  - 603 • For resistance analyses, any changes, including mixtures, in the amino acid sequence of  
604 the target protein, or DNA sequence for genome targeting drugs, present in on-treatment  
605 or follow-up samples, but not in the baseline sample, can be reported as having developed  
606 during therapy. In addition, baseline samples should be analyzed to identify HBV  
607 genetic polymorphisms that are associated with differential antiviral activity against the  
608 investigational drug. Sponsors should consult the FDA early for the most current format  
609 for submission of resistance data and if Next Generation Sequencing (NGS) will be used.  
610
  - 611 • There is a risk of the development of resistance against an antiviral drug that targets  
612 similar viral proteins in different virus species in patients coinfecting with HIV and HBV.  
613 Because of this risk, we recommend assessing for the development of resistance and  
614 cross-resistance in the viral proteins of both HIV-1 and HBV when appropriate.  
615
  - 616 • For all virologic assessments in clinical trials, we recommend the use of FDA-approved  
617 or FDA-cleared assays, when available, and a central laboratory. Sponsors can collect  
618 results from local lab tests, identifying the assay(s) used. If investigational assay(s) are  
619 used, performance characteristics of the assay(s) determined from analytical validation  
620 studies using geographically and temporally distinct isolates should be provided in  
621 addition to detailed descriptions of the methodology.<sup>17</sup> Drugs that require assays to  
622 identify the infected population benefiting from treatment (e.g., specific genotypes or  
623 resistant populations) may require a companion diagnostic. Additional recommendations  
624 can be found in the draft guidance for industry and FDA staff *Principles for*  
625 *Codevelopment of an In Vitro Companion Diagnostic Device With a Therapeutic*  
626 *Product*.<sup>18</sup>  
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<sup>17</sup> See the IDE (Investigational Device Exemption) web page available at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm>.

<sup>18</sup> When final, this guidance will represent the FDA's current thinking on this topic.

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- 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*

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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.

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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.

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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.

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- 667
- (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.

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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.

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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.

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**GLOSSARY OF ACRONYMS**

684		
685		
686	ALT	alanine aminotransferase
687	CC <sub>50</sub>	concentration inhibiting 50 percent cell growth
688	cccDNA	covalently closed circular DNA
689	CHB	chronic hepatitis B
690	EC <sub>50/90</sub>	effective drug concentration inhibiting 50 or 90 percent virus replication
691	FD&C Act	Federal Food, Drug, and Cosmetic Act
692	HBeAg	HBV enigma antigen
693	HBsAb	antibody specific to HBsAg
694	HBsAg	HBV surface antigen
695	HBV	hepatitis B virus
696	HBV DNA	hepatitis B virus DNA
697	HCC	hepatocellular carcinoma
698	HDV	hepatitis delta virus
699	HIV	human immunodeficiency virus
700	IFN	interferon
701	IgM	immunoglobulin M
702	IU	international unit
703	LLOQ	lower limit of quantification
704	mL	milliliter
705	NrtI	nucleoside/nucleotide reverse transcriptase inhibitor
706	NGS	Next Generation Sequencing
707	NI	noninferiority
708	PHH	primary human hepatocyte
709	PK	pharmacokinetic
710	qHBsAg	quantitative HBsAg
711	RNA	ribonucleic acid
712	rt	reverse transcriptase
713	SAP	statistical analysis plan
714	TND	target not detected
715	WHV	woodchuck hepatitis virus
716		

*Contains Nonbinding Recommendations*  
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**REFERENCES**

- 717  
718  
719 Alosch M, Fritsch K, Huque M, Mahjoob K, Pennello G, Rothmann M, Russek-Cohen E, Smith  
720 F, Wilson S, and Yue L, 2015, Statistical Considerations on Subgroup Analysis in Clinical  
721 Trials, *Stat Biopharm Res*, 7:286–304.  
722  
723 Arnold JJ, Sharma SD, Feng JY, Ray AS, Smidansky ED, Kireeva ML, Cho A, Perry J, Vela JE,  
724 Park Y, Xu Y, Tian Y, Babusis D, Barauskus O, Peterson BR, Gnatt A, Kashlev M, Zhong W,  
725 and Cameron CE, 2012, Sensitivity of Mitochondrial Transcription and Resistance of RNA  
726 Polymerase II Dependent Nuclear Transcription to Antiviral Ribonucleosides, *PLoS Pathog*,  
727 8(11):e1003030.  
728  
729 Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, Aguilar Schall R, Flaherty JF, Martins  
730 EB, Charuworm P, Kitrinis KM, Subramanian GM, Gane E, and Marcellin P, 2015, Seven-Year  
731 Efficacy and Safety of Treatment With Tenofovir Disoproxil Fumarate for Chronic Hepatitis B  
732 Virus Infection, *Dig Dis Sci*, 60:1457–1464.  
733  
734 Centers for Disease Control and Prevention, 2012, Case Definition Chronic Hepatitis B, accessed  
735 05/04/2018, <https://wwwn.cdc.gov/nndss/conditions/hepatitis-b-chronic/case-definition/2012/>.  
736  
737 Chan HL, Thompson A, Martinot-Peignoux M, Piratvisuth T, Cornberg M, Brunetto MR,  
738 Tillmann HL, Kao JH, Jia JD, Wedemeyer H, Locarnini S, Janssen HL, and Marcellin P, 2011,  
739 Hepatitis B Surface Antigen Quantification: Why and How to Use It in 2011 — A Core Group  
740 Report, *J Hepatol*, Nov, 55(5):1121–1131.  
741  
742 Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, Safadi R, Lee SS, Halota W, Goodman  
743 Z, Chi YC, Zhang H, Hindes R, Iloeje U, Beebe S, and Kreter B, 2010, Long-Term Entecavir  
744 Therapy Results in the Reversal of Fibrosis/Cirrhosis and Continued Histological Improvement  
745 in Patients With Chronic Hepatitis B, *Hepatology*, Sep;52(3):886–893.  
746  
747 Congly SE, Wong P, Al-Busafi SA, Doucette K, Fung SK, Ghali P, Fonseca K, Myers RP,  
748 Qsiowy C, and Coffin CS, 2013, Characterization of Hepatitis B Virus Genotypes and  
749 Quantitative Hepatitis B Surface Antigen Titres in North American Tertiary Referral Liver  
750 Centres, *Liver Int*, 99:1363–1369.  
751  
752 Forde KA, Tanapanpanit T, and Reddy R, 2013, Hepatitis B and C in African Americans:  
753 Current Status and Continued Challenges, *Clinical Gastroenterol Hepatol*, S1542–S3565 (13)  
754 000865-31.  
755  
756 Hu B, Wang R, Fu J, Su M, Du M, Liu Y, Li H, Wang H, Lu F, Jiang J, 2018, Integration of  
757 Hepatitis B Virus S Gene Impacts on Hepatitis B Surface Antigen Levels in Patients With  
758 Antiviral Therapy, *J Gastroenterol Hepatol*, 33(7):1389–1396.  
759  
760 Huang CR and Lo SJ, 2014, Hepatitis D Virus Infection, Replication and Cross-Talk With the  
761 Hepatitis B Virus, *World J Gastroenterol*, 20(40):14589–14597.  
762

***Contains Nonbinding Recommendations***

***Draft — Not for Implementation***

- 763 Lok AS, McMahon BJ, Brown RS, Jr., Wong JB, Ahmed AT, Farah W, Almasri J, Alahdab F,  
764 Benkhadra K, Mouchli MA, Singh S, Mohamed EA, Abu Dabrh AM, Prokop LJ, Wang Z,  
765 Murad MH, and Mohammed K, 2016, Antiviral Therapy for Chronic Hepatitis B Viral Infection  
766 in Adults: A Systematic Review and Meta-Analysis, *Hepatology*, 63:284–306.  
767
- 768 Lok AS, Zoulim F, Dusheiko G, and Ghany MG, 2017, Hepatitis B Cure: From Discovery to  
769 Regulatory Approval, *Hepatology*, 66(4):1296–1313.  
770
- 771 Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis  
772 G, Flaherty JF, Aguilar Schall R, Bornstein JD, Kitrinis KM, Subramanian GM, McHutchison  
773 JG, and Heathcote EJ, 2013, Regression of Cirrhosis During Treatment With Tenofovir  
774 Disoproxil Fumarate for Chronic Hepatitis B: A 5-Year Open-Label Follow-Up Study, *Lancet*,  
775 Feb 9;381(9865):468–475.  
776
- 777 Marroquin LD, Hynes J, Dykens JA, Jamieson JD, and Will Y, 2007, Circumventing the  
778 Crabtree Effect: Replacing Media Glucose With Galactose Increases Susceptibility of HepG2  
779 Cells to Mitochondrial Toxicants, *Toxicol Sci*, 97(2):539–547.  
780
- 781 Michalak TI, 1998, The Woodchuck Animal Model of Hepatitis B, *Viral Hepat, Rev.*, 4:139–  
782 165.  
783
- 784 Momper JD, Mulugeta Y, Green DJ, Karesh A, Krudys KM, Sachs HC, Yao LP, and Burckart  
785 GJ, 2013, Adolescent Dosing and Labeling Since the Food and Drug Administration  
786 Amendments Act of 2007, *JAMA Pediatr*, 167(10):926–32.  
787
- 788 Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, Calleja JL, Sypsa  
789 V, Goulis J, Manolakopoulos S, Loglio A, Siakavellas S, Keskin O, Gatselis N, Hansen BE,  
790 Lehretz M, de la Revilla J, Savvidou S, Kourikou A, Vlachogiannakos I, Galanis K, Yurdaydin  
791 C, Berg T, Colombo M, Esteban R, Janssen HLA, and Lampertico P, 2017, The Risk of  
792 Hepatocellular Carcinoma Decreases After the First 5 Years of Entecavir or Tenofovir in  
793 Caucasians With Chronic Hepatitis B, *Hepatology*, Nov;66(5):1444–1453.  
794
- 795 Roggendorf M and Tolle TK, 1995, The Woodchuck: An Animal Model for Hepatitis B Virus  
796 Infection in Man, *Intervirology*, 38:100–112.  
797
- 798 Schweitzer A, Horn J, Mikolajczyk RT, Krause G, and Ott JJ, 2015, Estimations of Worldwide  
799 Prevalence of Chronic Hepatitis B Virus Infection: A Systematic Review of Data Published  
800 Between 1965 and 2013, *Lancet*, 386:1546–1555.  
801
- 802 Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, and Murad MH, 2016, AASLD  
803 Guidelines for Treatment of Chronic Hepatitis B, *Hepatology*, 63:261–283.  
804
- 805 Thompson AJ, Nguyen T, Iser D, Ayres A, Jackson K, Littlejohn M, Slavin J, Bowden S, Gane  
806 EJ, Abbott W, Lau GK, Lewin SR, Visvanathan K, Desmond PV, and Locarnini SA, 2010,  
807 Serum Hepatitis B Surface Antigen and Hepatitis B E Antigen Titers: Disease Phase Influences

***Contains Nonbinding Recommendations***  
*Draft — Not for Implementation*

- 808 Correlation With Viral Load and Intrahepatic Hepatitis B Virus Markers, *Hepatology*, Jun,  
809 51(6):1933-1944.
- 810
- 811 World Health Organization Media Centre, 2017, Hepatitis D Fact Sheet, July, accessed  
812 05/04/2018, <http://www.who.int/mediacentre/factsheets/hepatitis-d/en/>.
- 813
- 814 Wranke A and Wedemeyer H, 2016, Antiviral Therapy of Hepatitis Delta Virus Infection —  
815 Progress and Challenges Towards Cure, *Curr Opin Virol*, 20:112–118.