



December 30, 2019

Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry
(FDA-2019-D-4042)

To the FDA:

On behalf of the Hepatitis B Foundation, a national nonprofit dedicated to education, advocacy and research to improve the lives of people living with hepatitis B and delta, we appreciate the opportunity to comment on the 'Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry' document recently released by FDA. The Hepatitis B Foundation's mission is to address the public health challenge of hepatitis B, and hepatitis delta through its dedicated program, *Hepatitis Delta Connect*. The program seeks to provide education, awareness, training, support for hepatitis delta researchers, physicians, the public, and patients; and to represent these voices in all matters related to hepatitis delta prevention, care and treatment.

We are pleased to see that FDA has prioritized providing guidance for industry on hepatitis delta drug development as we believe that the need for federal attention and serious investments to combat hepatitis delta in the U.S., and globally, is greater than ever.

We offer the following general comments on the document:

Suggested Change: Add Health-Related Quality of Life (QOL) Indicators

We urge FDA to consider the inclusion of health-related quality of life indicators as secondary outcomes – this is especially important for hepatitis delta, where we know patients often start out feeling poorly due to their disease (and can have side effects of treatment, too). Patients may be unwilling or unable to complete treatment regimens that negatively affect their mental and physical wellbeing due to side-effects of treatment. For example, most current patients are treated with pegylated interferon, a difficult protocol that can cause depression, anger, mood-swings. Future treatment developments should not only focus on effectiveness, but also on tolerability and impact on overall QOL.

Suggested Change: Add Need for Enrolling Diverse Patients

We urge industry to reach out to diverse U.S. populations for recruitment and inclusion in clinical trials, to ensure diversity (gender, ethnicity) and reach to foreign-born and hard to reach communities (including immigrant populations and people who use drugs). We suggest considering partnerships with community organizations to help reach these patients, as well as setting up clinical trial sites where these communities are, to ensure ease of access. Being inclusive of populations living in or having immigrated from Mongolia, Pakistan, the Eastern Mediterranean region (Romania, Turkey, Georgia), India, Brazil and West and Central Africa will be especially important. Thus, although we do not suggest this be required, wording emphasizing the importance and value of knowing outcomes in diverse populations is encouraged.

Suggested Change: Add Compassionate Use Indications

We suggest that FDA consider adding language around the need for industry to pursue compassionate use indications for their drugs, to deliver life-saving treatments to patients as early as possible. Many hepatitis delta patients are living with cirrhosis and will die in the years they must wait for these drugs to complete clinical trials and become commercially available. Compassionate use labeling can allow patients earlier access to drugs that could save their lives.

Suggested Change: Add Inclusion and Exclusion Criteria

We urge FDA to include a section within the guidance that outlines reasonable inclusion and exclusion criteria for eligible patients to enroll in clinical trials. For example, some current clinical trials exclude patients who have used interferon (the only currently available treatment) within the last year; this excludes many patients who are in desperate need of treatment options. Because pegylated interferon is the only treatment shown to be somewhat effective against hepatitis delta, most diagnosed patients have taking it off and on for years. This exclusion criteria punishes patients for treating their coinfection with best available treatments and prevents a large pool of patients from participating in potentially life-saving clinical trials. Allowing these patients to participate will improve participant recruitment and ethically, provide opportunity for these patients to access potentially life-saving treatment.

Suggested Change: Add Recommendations on Clinical Trial Accessibility

FDA should consider issuing guidance on industry considering the accessibility of clinical trial locations and urge them to cover travel/lodging expenses for patients who may not be within reasonable travel distance to their closest clinical trial site. The cost will be nominal compared to the benefits in increased enrollment, subsequent data, and will improve access for patients with limited resources.

Suggested Change: Add Language Emphasizing Role Between Hepatitis B and Delta Viruses

Within the document, we find that there is a lack of emphasis on the interplay between hepatitis B and hepatitis delta during monotherapy of each virus. It is important to add language around the interconnected role the viruses have with one another and need for combination therapy to attempt to control both viruses simultaneously.

Suggested Change: Consider Removal of Placebo Controls, Consider Pegylated Interferon as “Standard of Care”

Given the current lack of approved therapies for hepatitis B and delta coinfection and the more rapid progression to liver disease in these participants, even while on nucleoside (NUC) monotherapy, the FDA should consider the ethical implications of requiring a placebo control. Interferon alpha therapy, with or without NUC therapy can be well tolerated among co-infected patients and can have clinical benefit (Wedemeyer et al., 2019). Interferon therapy is the only treatment found to be even somewhat effective for some patients in reducing hepatitis delta viral load, normalizing ALT and lessening liver damage (Ciancio et al., 2011, Abbas, et al 2014) and should be considered the “standard of care”. In considering biomedical research ethics, allowing placebo control arms within these trials presents an ethical problem, denying patients access to the “best proven intervention”. Additionally, clinical trial recruitment and completion can be improved with a non-placebo control arm. Inclusion of a crossover design could be an additional option, allowing those in the placebo arm to benefit from experimental therapy after a set time period, especially if there is early positive response in the experimental arm.

Comments by line:

Line 57-58: Consider Adding Additional Information about Hepatitis Delta Prevalence

We suggest adding language about the limitations of using NHANES data to estimate hepatitis delta prevalence, as NHANES does not adequately represent communities most likely to be impacted. We suggest adding language acknowledging that the data from current surveillance efforts are limited. We also suggest adding statistics from other published studies suggesting different prevalence estimates. For example, the Martins et. al prevalence analysis in U.S. using 2016 ICD-9 and ICD-10 guided methodology estimates there are ~100,000 patients chronically infected with HDV (Martins, et al 2017). Additionally, guidance documents from countries such as Germany support testing all patients who are positive for HBsAg.

Line 66: Add Emphasis on Hepatitis Delta's Poor Antiviral Response

It should be emphasized that hepatitis B and delta coinfecting patients have poor clinical responses to hepatitis B antiviral therapy, since liver damage can be predominantly caused by hepatitis delta virus infection (Wedemeyer et al., 2011). Therefore, after hepatitis B therapy, not only does delta infection persist, but so does the chronic liver disease.

Lines 67-69: Add Emphasis on Limitations of Currently Available Treatment; Interferon

We suggest adding language regarding the limited use and limited benefit of using pegylated interferon for treatment of hepatitis delta, as evidence for the need for new and more effective treatment options.

Lines 187-189: Inclusion of U.S. Patients in Clinical Trials Should be Encouraged but Not Required

We believe it is ideal to include participants from U.S. populations, especially those most impacted by hepatitis B and hepatitis delta coinfection. This will ensure that those populations most impacted in the U.S. will have the opportunity to be represented in clinical trials and that treatment-related outcomes data will be collected from them. However, if sufficient quality and reliability can be demonstrated with non-US study, this should not be required.

Lines 345-347: Clinical Endpoints

While there is no clear agreement currently on clinical endpoints for HDV treatment, popular scientific opinion suggests that reduction of HDV RNA (sustained, off treatment) should suffice. Additionally, it is believed that if a patient achieves negative HDV RNA but ALT levels are elevated, the lack of biochemical response is likely not related to HDV related disease - but rather to other diseases such as HBV, NASH, NAFLD, alcohol-related hepatitis or advanced liver disease. We suggest the treatment endpoints remain separate; with the primary endpoint the virologic endpoint (HDV RNA reduction) and the secondary endpoint normalization of ALT. A recently published report in Journal of Hepatology suggests that some experts believe using a 2-log reduction of HDV RNA can serve as the primary endpoint for treatment efficacy, while others believe that undetectable HDV RNA should be the endpoint for finite treatment (Cornberg et al., 2019; Yurdaydin et al., 2019).

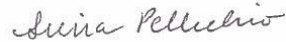
We thank you for this opportunity to comment on the draft guidance as we strongly support these guidelines issued by FDA on hepatitis delta drug development. We believe that FDA's guidance and recommendations are vital to ensuring the timely, effective, and ethical development of new treatments for hepatitis delta patients.

Thank you for taking the time to consider our comments. Please do not hesitate to contact Chari Cohen, at (chari.cohen@hepb.org) with any questions.

Sincerely,



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Literature Cited

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