FDA Guidance on Less Common Viral Hepatitis Type

The US Food and Drug Administration (FDA) recently revisited the topic of drugs for liver infection through a newly issued guidance document on hepatitis D virus (HDV).

In October 2019, the FDA released the draft guidance for industry, *Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment,* which provides the agency's current recommendations regarding the overall development programme and clinical trial designs for the development of drugs and biologics to support an indication for the treatment of chronic HDV infection. In November 2018, the agency released the draft guidance, *Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment*, which contains information relevant to HDV drug development, but focuses on drugs and biologics to treat chronic hepatitis B virus (HBV) infection.

The Centers for Disease Control and Prevention (CDC) explains that infection by HDV (also known as hepatitis delta virus) is uncommon in the US, occurring only in people who are infected with HBV. This is because HDV is a replication-defective virus that uses the HBV surface antigen (HBsAg) as its envelope protein. Therefore, HDV infection only occurs in the setting of concurrent HBV infection.

In July 2019, the World Health Organization (WHO) noted that at least 5% of people with chronic HBV infection are co-infected with HDV, resulting in a total of 15-20 million persons infected with HDV worldwide. However, the WHO stated, this is a broad global estimate since many countries do not report the prevalence of HDV.

According to the WHO, HDV-HBV co-infection is considered the most severe form of chronic viral hepatitis due to more rapid progression toward liver-related death and hepatocellular carcinoma. HDV is transmitted via the same routes as HBV: percutaneously or sexually through contact with infected blood or blood products. HDV infection can be an acute, short-term infection or a long-term, chronic infection. Vaccination against HBV prevents HDV co-infection, and hence expansion of childhood HBV immunisation programmes has resulted in a decline in hepatitis D incidence worldwide, the WHO states.

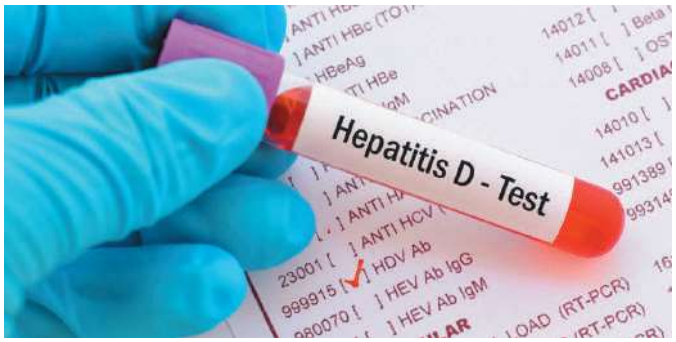
Drug Development Programmes

In its October 2019 guidance, the FDA noted that because chronic HDV infection is considered serious and life-threatening and there are no approved treatments, investigational anti-HDV drugs may be eligible for the FDA's expedited programmes, such as fast track, breakthrough therapy, and priority review designations. Given that trials demonstrating clinical benefit of an HDV therapy would likely require a prolonged follow-up period, the FDA anticipates that development programmes may opt to pursue accelerated approval pathways based on a surrogate endpoint.

According to section 507(e)(9) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the term 'surrogate endpoint' is defined as "a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and —

(A) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or
(B) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in accordance with section 506(c)."

As explained by the FDA, clinical trials are needed to show that surrogate endpoints can be relied upon to predict, or correlate with, clinical benefit. Surrogate endpoints that have undergone this testing are called validated surrogate endpoints and these are accepted by the FDA as evidence of benefit.



For HDV infection, no surrogate endpoints have been definitively shown to predict clinical benefit, the FDA stated in the October 2019 guidance. An appropriate surrogate endpoint for the treatment of HDV should provide evidence of both a decline in virologic replication and an improvement in associated liver inflammation as evident by biochemical response, the agency explained. As precedent, the agency noted in the November 2018 guidance that HBV DNA suppression with or without HBsAg loss is considered a validated surrogate endpoint that has been demonstrated to predict clinical outcomes, and that this endpoint could be used to support a traditional approval.

Regarding drug development programmes in general, the FDA advises that they should include a diverse and representative clinical trial population. In the October 2019 guidance, the FDA pointed to the global presence of HDV infection, with the greatest burden of infection occurring in Eastern and Mediterranean Europe, the Middle East, the Amazon Basin, and parts of Asia and Africa. Sponsors are advised to consider the following points in relation to trial populations:

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

- Eligibility criteria should allow the clinical trial population to reflect the diversity of the patients who will be using the drug if it is approved, the FDA said. For additional information, see the draft guidance for industry, *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs*, issued in June 2019.

The FDA accepted public comments on the October 2019 draft guidance to Docket No. FDA–2019–D–4042 until December 31, 2019.

Deborah Komlos

Deborah Komlos, MS, is the Senior Medical & Regulatory Writer for the Cortellis suite of life science intelligence solutions at Clarivate Analytics. In this role, her coverage centres on FDA advisory committee meetings, workshops, and product approvals. Her previous positions have included writing and editing for magazines, newspapers, online venues, and scientific journals, as well as publication layout and graphic design work.

Email: deborah.komlos@clarivate.com