Protocol (CeSHarP).'' The notice gave interested persons an opportunity to submit comments by February 21, 2023.

In the **Federal Register** of June 6, 2025 (90 FR 24146), FDA published a notice announcing the availability of a revised draft guidance entitled ''M11 Technical Specification: Clinical Electronic Structured Harmonised Protocol.'' The notice gave interested persons an opportunity to submit comments by July 7, 2025.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Assembly and endorsed by the regulatory agencies in November 2025.

This guidance finalizes the draft guidances issued on December 22, 2022, and June 6, 2025. The guidance provides harmonized and comprehensive technical recommendations for clinical trial protocol through three key documents: the guidance, which provides the rationale and recommendations for implementing a harmonized digital clinical trial protocol; a standardized protocol template featuring standardized content structure and formatting, including headers and common text elements; and a technical specification document containing harmonized terminologies and standardized data fields to enable electronic exchange of clinical protocol information. Revisions were made to all documents addressing public comments and providing greater clarity to key terms and scope.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on ''M11 Clinical Electronic Structured Harmonised Protocol (CeSHarP).'' 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.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521). The collections of information in 21 CFR part 312 pertaining to clinical trial design and protocols have been approved under OMB control number 0910–0014.

III. Electronic Access

Persons with access to the internet may obtain the guidance at *https://www.regulations.gov*, *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances,* or *https://www.fda.gov/regulatory-information/search-fda-guidance-documents.*

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

[FR Doc. 2026–10295 Filed 5–21–26; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–N–0567]

Notice of Decision Not To Designate Hepatitis Delta Virus Diseases as an Addition to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: In response to a suggestion by Gilead Sciences, Inc. (Gilead) that was submitted to the public docket FDA–2008–N–0567 on February 14, 2022, the Food and Drug Administration (FDA or Agency) has analyzed whether hepatitis delta virus (HDV) infection meets the statutory criteria for designation as a ''tropical disease'' under Section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Specifically, the Agency has analyzed whether there is ''no significant market in developed nations'' for drugs for HDV infections and whether HDV ''disproportionately affects poor and marginalized populations,'' both of which are statutory criteria for designation as a ''tropical disease.'' At this time, the Agency cannot conclude that HDV infection meets the statutory criteria for addition to the list of tropical diseases under the FD&C Act; therefore, FDA declines to add it to the list of tropical diseases.

DATES: May 22, 2026.

ADDRESSES: Submit electronic comments on additional diseases suggested for designation to *https://www.regulations.gov.* Submit written comments on additional diseases suggested for designation to the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Sunita Shukla, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6334, Silver Spring, MD 20993–0002, 301–796–6406, *Sunita.Shukla@fda.hhs.gov;* or Phillip Kurs, Center for Biologics Evaluation and Research, Food and Drug Administration, 240–402–7911.

SUPPLEMENTARY INFORMATION:

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I. Background: Priority Review Voucher Program

Section 524 of the FD&C Act (21 U.S.C. 360n), which was added by section 1102 of the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110–85), uses a priority review voucher (PRV) incentive to encourage the development of new drugs, including biological products, for prevention and treatment of certain diseases that, in the aggregate, affect millions of people throughout the world. To be eligible to receive a tropical disease PRV, a sponsor must submit a human drug application that is for prevention or treatment of a ''tropical disease'' as listed under section 524(a)(3) of the FD&C Act. This list can be expanded by the Agency under section 524(a)(3)(S) of the FD&C Act, which authorizes FDA to designate by order ''[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations'' as a ''tropical disease.'' Further information about the tropical disease PRV program can be found in the guidance for industry ''Tropical Disease Priority Review Vouchers,'' issued on October 6, 2016 (81 FR 69537), and available at *https://www.fda.gov/media/72569/download.* Additions to the statutory list of tropical diseases by an FDA final order published in the **Federal Register**

can be accessed at *https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program.*

On August 20, 2015, FDA published a final order (80 FR 50559) (August 2015 final order) designating Chagas disease and neurocysticercosis as additions to the list of tropical diseases under section 524 of the FD&C Act. The August 2015 final order also set forth FDA's interpretation of the statutory criteria for designation as a tropical disease under section 524(a)(3)(R) of the FD&C Act (redesignated as section 524(a)(3)(S) of the FD&C Act).

As explained in the August 2015 final order, FDA uses the World Bank's list of ''high-income economies'' as evidence that a country should be considered a ''developed nation'' for purposes of tropical disease designation (Ref. 1). In the August 2015 final order, FDA stated that it interprets the statutory criterion ''no significant market'' (within the phrase ''no significant market in developed nations'' under section 524(a)(3)(S) of the FD&C Act) to refer to the market for drugs for the treatment or prevention of infectious diseases. The August 2015 final order states, ''[b]ecause the statute offers vouchers for applications for drugs for either the treatment or prevention of infectious diseases, it is reasonable to assume that 'no significant market' can refer to drugs for the treatment or prevention of infectious diseases.'' 80 FR at 50560.

In the August 2015 final order, FDA explained that it agrees with the use of an overall flexible approach to tropical disease designation and notes that ''[t]he purpose of section 524 of the FD&C Act is to provide an incentive for innovation where there otherwise would be an insufficient financial or market incentive to invest in developing drugs for tropical diseases''. Id. To determine whether a ''significant market'' exists in developed nations, FDA considers both the direct and the indirect market for drugs for the treatment or prevention of a particular infectious disease. As noted in the August 2015 final order, the direct market reflects ''situations in which individuals (often reimbursed by their insurers) purchase the products for use by a specific patient,'' and ''the direct market for a drug in a developed country can often be estimated by assessing the occurrence of a particular disease in that country.'' 80 FR at 50560–61. Further, as described in the August 2015 final order, FDA uses a disease prevalence rate of 0.1 percent of the population in developed countries for aiding in the determination of whether a significant market may exist for treatment of a disease. In addition to disease prevalence, other factors have been considered by FDA, including, for example, the incidence of the disease. Incidence measures new cases that are diagnosed in a population in a given time period. FDA also considers whether there is a sizable indirect market for a drug for the treatment or prevention of an infectious disease, which could be comprised of government entities or nongovernmental organizations that wish to purchase and distribute a drug.

As discussed below, the Agency has determined that it cannot conclude at this time that HDV meets the statutory criteria for designation as a ''tropical disease'' under section 524 of the FD&C Act; thus, FDA will not add it to the list of tropical diseases for which a human drug application may be eligible for a PRV.

II. Decision Not To Designate Hepatitis Delta Virus Infection

Based on an assessment of currently available information, FDA has determined that HDV will not be designated as a ''tropical disease'' under section 524 of the FD&C Act.

A. Background

HDV infection, also known as ''delta hepatitis,'' is a liver infection caused by HDV, a defective RNA virus that requires hepatitis B virus (HBV) surface antigen (HBsAg) for replication and transmission (Ref. 2, Ref. 3, Ref. 4). Thus, HDV infection only occurs in individuals also infected with HBV and can be acute or chronic. Chronic HDV/HBV infection is the most severe form of chronic viral hepatitis, with more rapid progression to cirrhosis, hepatocellular carcinoma, and death (Ref. 5). Cohort studies show the risk of adverse liver-related outcomes may be 9 times higher in patients with chronic HDV/HBV infection than in those with HBV monoinfection (Ref. 6), with greater likelihood of liver transplantation (Ref. 7). On average, HDV/HBV infection progresses to cirrhosis within 5 years and to hepatocellular carcinoma within 10 years (Ref. 8).

An estimated 1.59 million persons (range 1.25–2.49 million) live with chronic HBV infection in the United States (Ref. 9) and 254 million (range 224.0–286.6 million) globally (Ref. 10). These people are at potential risk of HDV infection. Estimated HDV prevalence rates reported in the literature vary widely, in part because of different methodologies used but also because of historically low levels of HDV testing. The presence of anti-HDV antibodies identifies HBsAg-positive individuals who have been exposed to HDV (either in the past or due to ongoing infection); however, detection of HDV RNA is needed to confirm active HDV infection. Chronic HDV (CHD) infection is defined by detectable HDV RNA in the blood for at least six months.

As noted above, HDV prevalence estimates vary widely. Some reports suggest HDV infection may affect 12.0 million people worldwide (95% CI, 8.7–18.7) (Ref. 11, Ref. 12, Ref. 13). A meta-analysis estimated a 4.5% (95% CI, 3.6–5.7) anti-HDV (*i.e.,* total or IgG anti-HDV antibodies) prevalence rate among HBsAg-positive persons and 16.4% (95% CI, 14.6–18.6) among those attending hepatology clinics (Ref. 13). Other meta-analyses estimated 13.0% (95% CI, 12.0–14.1) HDV infection prevalence among HBV carriers and 0.80% (95% CI, 0.6–1.0) in the general population, corresponding to 48–60 million HDV infections globally (Ref. 8).

Higher HDV rates are observed in low- and middle-income countries, with highest rates reported in Mongolia, Brazil, the Republic of Moldova, and countries in Western and Middle Africa (Ref. 14, Ref. 13). Higher rates are also reported in people who inject drugs (PWID), hemodialysis recipients, men who have sex with men, commercial sex workers, and those living with hepatitis C virus (HCV) or human immunodeficiency virus (HIV) (Ref. 15, Ref. 13, Ref. 16). In high-income countries, a substantial proportion of HDV infections are found in immigrant populations (Ref. 17, Ref. 18). For example, foreign-born persons were reported to contribute more than 50% of the HDV infection burden in both Greece and Germany (Ref. 17). An Italian study reported that while the rate of anti-HDV antibody positivity in Italy had declined among native-born Italians, there was a 6-fold increase among people born abroad (Ref. 19). Meanwhile, in a study of chronic viral hepatitis infections among people of Mongolian descent in Southern California, all but three of whom were foreign-born, the anti-HDV antibody prevalence rate was 39.6% and HDV RNA positivity was 34.0% among those with chronic HBV infection, rates that are as high as those reported in Mongolia (Ref. 20).

Given the dependence of HDV on HBV for its propagation, the most effective means of HDV prevention is HBV vaccination. Hepatitis B immunization, however, does not protect against HDV in those already chronically infected with HBV. By 2024, global coverage of three infant doses of the hepatitis B vaccine reached 84%

(Ref. 21, Ref. 22). In the United States, adult HBV vaccination coverage was reported as 30–33% (Ref. 23 (discussing the standard recommended 3-dose vaccine coverage), Ref. 24 (discussing having received at least one vaccine dose)).[1] In response, in 2022, the Advisory Committee on Immunization Practices (ACIP) recommended universal hepatitis B vaccination for all U.S. adults aged 19 through 59 years (Ref. 25), in contrast to previous recommendations that were risk-factor based. As of March 2026, the Centers for Disease Control and Prevention (CDC) continues to recommend universal HBV vaccination for all adults aged 19 through 59 years, with shared clinical decision-making for adults aged 60 years or older (Ref. 26).

Therapeutic options for CHD are limited. Nucleos(t)ide analogues, such as tenofovir disoproxil fumarate, entecavir, and tenofovir alafenamide, are first-line HBV treatments but ineffective against HDV, either alone or in combination with pegylated interferon-α (Peg-IFNα) (Ref. 27, Ref. 28, Ref. 29).

In the United States, there is no FDA-approved treatment for CHD. Pegylated interferon-α has been endorsed by some treatment guidelines (Ref. 27, Ref. 30), but many HDV patients are ineligible due to advanced liver disease or contraindications. In addition, Peg-IFNα therapy causes adverse side effects, such as flu-like symptoms, anemia, neutropenia, and thrombocytopenia, resulting in poor tolerability and high discontinuation rates (Ref. 31). Moreover, response rates are variable, ranging from 17% to 35%, and relapses are common (Ref. 32, Ref. 33, Ref. 5). Outside the United States, bulevirtide (Hepcludex® in the European Economic Area [EEA], United Kingdom [UK], Switzerland, and Australia; Myrcludex B® in Russia) is approved for CHD treatment in adults with compensated liver disease. To date, FDA has not approved bulevirtide for treatment of CHD.

B. No Significant Market in Developed Nations

It cannot be concluded that there is no significant market in developed nations for drugs to treat or prevent HDV infection.

As noted above, FDA is authorized to designate certain diseases as tropical diseases if certain criteria are met. The first criterion is that ''there is no significant market in developed nations.'' As stated in the August 2015 final order, FDA intends to use a country's presence on the World Bank list of ''high income economies'' as evidence that the country should be considered a ''developed nation'' for ''tropical disease'' determination purposes (80 FR at 50560).

In the August 2015 final order, FDA further explains that it agrees with the use of an overall flexible approach to tropical disease designation and notes that ''[t]he purpose of section 524 of the FD&C Act is to provide an incentive for innovation where there otherwise would be an insufficient financial or market incentive to invest in developing drugs for tropical diseases''. Id. FDA explains that it ''will analyze the market for drugs for both the treatment and prevention of infectious diseases.'' Id. FDA further identifies factors to consider in determining whether a ''significant market'' exists in developed countries. First, FDA explains that there are ''direct'' markets—that is, markets in which patients purchase drugs for their own use. Id. In discussing the direct market, FDA identifies one relevant factor, disease prevalence, explaining that ''if the prevalence of a disease in developed countries is less than 0.1 percent of the population of those countries, it is unlikely that ordinary market forces will offer a sufficient incentive to drive the development of new preventions or treatments.'' Id. at 50561. Other factors have been considered by FDA, including, for example, the incidence of the disease. See 85 FR 42860 (July 15, 2020) (designating brucellosis); 85 FR 42871 (July 15, 2020) (declining to designate coccidioidomycosis); 80 FR 50559 (Aug. 20, 2015) (designating neurocysticercosis); and 83 FR 42904 (Aug. 24, 2018) (designating rabies). Second, FDA states in the August 2015 final order that ''some drugs may have a sizeable 'indirect market' composed of, for example, government entities or nongovernmental organizations that wish to purchase and distribute a drug for the treatment or prevention of an infectious disease, which could be relevant to the analysis, as well. Id.

The literature suggests that HDV infection prevalence is higher among low- and lower-middle-income countries compared to high-income countries, and disproportionately affects countries in regions such as Africa, Central and South Asia, and Oceania that are included in the World Bank list of low-income economies (Ref. 15, Ref. 13). Gilead provided Table 1 below to show prevalence rates of HDV infection among 8 countries included on the World Bank list of high-income economies (Ref. 52).

TABLE 1—SUMMARY OF PERCENT HDV INFECTION PREVALENCE IN THE GENERAL POPULATION IN HIGH INCOME ECONOMIES

High-income economies	(%) Prevalence in general population *	(95% CI)
Australia	0.01	(0.0, 0.02).
France	0.01	(0.004, 0.01).
Germany	0.02	(0.01, 0.03).
Italy	0.02	(0, 0.1).
Japan	0.70	(0.5, 0.9).
Saudi Arabia	0.10	(0.01, 0.2).
United Kingdom	0.02	(0.001, 0.1).
United States	0.02	(0.01, 0.03).

Source: Gilead's Tropical Disease Designation Request (Ref. 52, based on Ref. 13).
* Prevalence represents the country-level anti-HDV prevalence in the total population.

Of note, Gilead purports that the higher HDV infection prevalence rate in Japan (0.70%) is likely an over-estimation given that the limited data obtained from two small studies in a remote region of Japan are likely not

[1] The U.S. Census Bureau reports the total population in the United States per the 2020 Decennial Census is 331,449, 281 (see Ref. 49), and estimates the total population in the United States as of July 1, 2025 to be 341,784,857 (see Ref. 50). Additionally, the U.S. Census Bureau estimates that 21.5% of the U.S. population is under 18 years of age, and that 14.1% of the U.S. population between 2020–2024 are foreign-born persons (see Ref. 50).

representative of the overall population. The basis for this assertion, however, is unclear.

It is notable that there are additional countries on the World Bank list of high-income economies not included in the above table (many of which do not have published HDV prevalence rates). For instance, Romania is a high-income country and has an HDV prevalence in the general population of 0.4% (95% CI, 0.1–1.5) (Ref. 13).

Published literature also indicates that the estimated prevalence of HDV infection in the United States is possibly higher than reported by Gilead in Table 1. Determining U.S. HDV prevalence is challenging for several reasons. First, HDV screening is not routine and testing rates among chronic HBV patients are suboptimal. For example, a Veterans Affairs study found that less than 8% of HBsAg-positive patients had been tested for HDV (Ref. 34). Second, HDV infection is not a nationally notifiable condition, so the actual number of U.S. cases is unknown according to the CDC (Ref. 35). A 2019 review found anti-HDV antibody positivity among U.S. HBsAg-positive carriers ranged from 2% to 50%, depending on the population sampled (Ref. 36). Reference 13, which is relied on by Gilead in Table 1, above, acknowledges limited North America data and variable U.S. HDV prevalence estimates.

A National Health and Nutrition Examination Survey (NHANES) study, using data from 2011 through 2016, reported anti-HDV antibody prevalence of 0.11% (95% CI, 0.08–0.17) in the overall U.S. population aged ≥ 6 years and 0.15% (95% CI (0.10–0.23) among adults aged ≥ 18 years (Ref. 37). These rates are markedly higher than those noted by Gilead in Table 1 (Ref. 13). It is also worth noting that NHANES data may underrepresent foreign-born persons (Ref. 38), who drive HDV prevalence in developed nations including the United States, suggesting that actual U.S. prevalence may be higher.

More recent publications continue to report varying HDV prevalence in the United States and other high-income countries, though these too may underestimate true prevalence due to limited clinical recognition of HDV and testing. A study using an All-Payer Claims Database estimated 4.6% HDV prevalence among HBV patients in the United States from 2015 to 2019 (Ref. 39). A retrospective study of three U.S. urban safety-net health systems from 2010 to 2022 found that 15.7% of tested chronic HBV patients were anti-HDV antibody positive, though only 6.1% of chronic HBV patients were tested for HDV, and among those tested, only two patients (1.6%) received follow-up HDV RNA testing (Ref. 40).

A literature review and meta-analysis using 2022 U.S. Census Bureau data estimated a weighted average HDV prevalence of 4.2% among foreign-born persons with chronic HBV infection (64,938 persons [95% CI 33,055–97,392]), and a total of 1.97 million (95% CI 1.547–2.508) persons living with chronic HBV and 75,005 (95% CI 42,187–108,393) persons living with HDV in the United States in 2022 (Ref. 41). In Canada, a similar analysis using 2021 Statistics Canada data estimated the weighted average HDV prevalence among foreign-born persons with chronic HBV infection at 5.19% (17,848 persons [95% CI 9,611–26,052]), with an estimated 0.55 million (95% CI 0.488–0.615) persons living with chronic HBV and 35,059 (95% CI 18,744–52,083) persons living with HDV in 2021 (Ref. 42).[2] In Italy, a 2024 study estimated HDV prevalence at 7.7% among adults with chronic HBV infection and 0.019% in the general population (Ref. 43).

The available HDV prevalence data have significant limitations, chief among them is the undertesting of chronic HBV patients for HDV. In addition, methodological differences across published studies, the use of estimated rates with wide variability, and reliance on anti-HDV antibody data with a lack of HDV RNA data can all potentially result in over- or under-estimation of true HDV prevalence. Given the data discussed above, these limitations, and the reported variability, in several high-income economies, it cannot be concluded that HDV prevalence is less than 0.1%.

Beyond prevalence data, evidence exists for a direct market for HDV drugs. Notably, bulevirtide is approved as Hepcludex® in the EEA, UK, Switzerland, and Australia, and as Myrcludex B® in Russia, for the treatment of CHD in adults with compensated liver disease. Bulevirtide received conditional Marketing Authorization (MA) from the European Commission in July 2020 and converted to full MA in July 2023. The UK conditional MA converted to full MA in August 2023, and Switzerland granted full MA in February 2024 (Ref. 44).

Available bulevirtide sales data are limited. Early reports from Gilead noted bulevirtide contributed $7 million in Q2 2021 following initial European approval in July 2020 (Ref. 45). According to Gilead's Fourth Quarter and Full Year 2025 Financial Results, ''The Liver Disease portfolio sales increased 6% to $3.2 billion in the full year 2025 compared to 2024, primarily driven by higher demand for Livdelzi and products for chronic hepatitis B virus (''HBV'') and chronic hepatitis delta virus (''HDV''), partially offset by lower average realized price in products for chronic hepatitis C virus (''HCV'')'' (Ref. 46). Hepcludex® (bulevirtide) sales are not reported separately, making it difficult to determine its specific contribution.

Additionally, according to *clinicaltrials.gov,* there are several investigational agents for the treatment of chronic HDV that have ongoing or completed Phase 3 trials, including pegylated interferon lambda-1a, lonafarnib/ritonavir, tobevibart plus elebsiran, brelovitug, and hepalatide.

A preventive product developed specifically for HDV infection would likely find a direct market given the estimated 1.59 million persons (range 1.25–2.49 million) living with chronic HBV infection in the United States (Ref. 9) and 254 million (range 224.0—286.6 million) globally (Ref. 10). Patel et al. estimated HBsAg prevalence of 0.36% (95% CI 0.29–0.46) among U.S. adults aged ≥18 years, indicating a sizeable patient population with chronic HBV infection that could benefit from measures to prevent HDV superinfection (when a person with chronic HBV infection becomes newly infected with HDV) (Ref. 37).

Regarding an indirect market, HDV is not on the CDC list of potential bioterrorism agents. Gilead states they are unaware of any significant U.S. government funding for HDV drug development. Consistent with this, the Viral Hepatitis National Strategic Plan 2021–2025 focuses only on hepatitis A, B, and C (Ref. 47). Thus, no apparent ''indirect'' market exists for HDV treatment or prevention within the United States.

In summary, literature evidence suggests HDV prevalence exceeds 0.1% in several high-income countries, including Japan, Romania, Saudi Arabia, and possibly the United States, though variability exists in reported rates, likely due to inconsistent and suboptimal HDV testing. Other evidence for a direct treatment market includes bulevirtide's approval in several developed nations and Phase 3 clinical trials of investigational agents listed on *clinicaltrials.gov*. Evidence for a direct prevention market includes consistently reported chronic HBV infection rates well above 0.1% in the United States. Although hepatitis B vaccination prevents both HBV and HDV infection,

[2] The Government of Canada reports the total population of Canada per the 2021 census data to be 36,991,981 (see Ref. 51).

HBV vaccine coverage remains underutilized in the United States. Because patients with chronic HBV infection are at risk for HDV superinfection, a preventative product for this patient population would find a sizeable market if developed. Although no apparent indirect market exists for HDV treatments or preventions within the United States, this does not outweigh the direct market evidence. Therefore, it cannot be concluded that no significant market exists in developed nations for treatment or prevention of HDV infection.

C. Disproportionately Affects Poor and Marginalized Populations

The relative burden of HDV infection has been reported to be greatest amongst impoverished and marginalized populations. In a systematic review and meta-analysis, Chen et al. summarized the association between sociodemographic development index (SDI), a composite indicator of development status correlated with health outcome, and HDV prevalence from 61 countries and found that immigrant populations from countries with low SDI were associated with higher HDV prevalence (Ref. 17). Further, disproportionately higher rates of HDV persist in other marginalized populations, such as in PWID, people living with HIV or HCV, and people with high-risk sexual behaviors (Ref. 15, Ref. 13, Ref. 16).

While HDV infection has not been designated by the WHO as a neglected tropical disease, a panel of scientists and public health experts from academia and the WHO published a study in the Journal of Hepatology in 2020 (Ref. 13, Ref. 48) highlighting the need to improve the response to HDV. When discussing this study, one of the co-authors stated that ''HDV has long been neglected, because for decades the prevalence of infection remained uncertain and effective treatment was lacking.'' (Ref. 48).

D. FDA's Determination

In conclusion, based on the totality of available data, HDV infection does not currently meet the statutory criteria to be designated by order as a tropical disease under section 524 of the FD&C Act. While HDV infection ''disproportionately affects poor and marginalized populations,'' it cannot be concluded that ''there is no significant market in developed nations'' for treatment and prevention of HDV infection.

III. Process for Requesting Additional Diseases To Be Added to the List

FDA's current determination regarding HDV infection does not preclude interested persons from requesting its consideration in the future as additional new data become available. To facilitate the consideration of future additions to the list, FDA established a public docket (see *https://www.regulations.gov,* Docket No. FDA–2008–N–0567) through which interested persons may submit requests for additional diseases to be added to the list. Such requests should be accompanied by information to document that the disease meets the criteria set forth in section 524(a)(3)(S) of the FD&C Act. FDA will periodically review these requests, and, when appropriate, expand the list. For further information, see FDA's Tropical Disease Priority Review Voucher Program web page at *https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program.*

IV. Paperwork Reduction Act

This notice reiterates the ''open'' status of the previously established public docket through which interested persons may submit requests for additional diseases to be added to the list of tropical diseases that FDA has found to meet the criteria in section 524(a)(3)(S) of the FD&C Act. Such a request for information is exempt from Office of Management and Budget review under 5 CFR 1320.3(h)(4) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). Specifically, ''[f]acts or opinions submitted in response to general solicitations of comments from the public, published in the **Federal Register** or other publications, regardless of the form or format thereof'' are exempt, ''provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of the full consideration of the comment.''

V. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**,but websites are subject to change over time.

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Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–D–2424]

Protein Efficiency Ratio Rat Bioassay Studies To Demonstrate That a New Infant Formula Supports the Quality Factor of Sufficient Biological Quality of Protein; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or we) is announcing the availability of a guidance entitled ''Protein Efficiency Ratio (PER) Rat Bioassay Studies to Demonstrate That a New Infant Formula Supports the Quality Factor of Sufficient Biological Quality of Protein.'' The guidance provides information for manufacturers and contract laboratories that perform PER studies to assist in designing, conducting, evaluating, and reporting PER studies. The guidance explains ''appropriate modifications'' of AOAC Official Method 960.48 (the AOAC Method) with the aim of supporting industry in successfully conducting PER studies that demonstrate that a new infant formula meets the quality factor of sufficient biological quality of protein when fed as the sole source of nutrition. The guidance finalizes the approach presented in the draft guidance issued in 2023.

DATES: The announcement of the guidance is published in the **Federal Register** on May 22, 2026.

ADDRESSES: You may submit either electronic or written comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2022–D–2424 for ''Protein Efficiency Ratio (PER) Rat Bioassay Studies to Demonstrate That a New Infant Formula Supports the Quality Factor of Sufficient Biological Quality of Protein.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the guidance to Office of Critical Foods, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740. Send one self-addressed adhesive label to assist that office in processing your request or include a Fax number to which the guidance may be sent. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the guidance.

FOR FURTHER INFORMATION CONTACT: *With regard to the guidance:* Ariel Bourne, Office of Critical Foods, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–1450, email: *Ariel.Bourne@fda.hhs.gov;* or Barbara Little, Office of Policy and International Engagement, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–8808.

With regard to the proposed collection of information: Michael Ellison, Office of Operations, Food and Drug Administration, Three White Flint North, 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 240–402–2093, *PRAStaff@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry titled ''Protein