Commonwealth of Independent States (CIS). The FAA is issuing this AD to address the reassessment of these repairs. The unsafe condition, if not addressed, could lead to damage or failure of the affected parts and the NLG, and possible damage to the airplane and injury to occupants.

(f) Compliance

Comply with this AD within the compliance times specified, unless already done.

(g) Requirements

Except as specified in paragraph (h) of this AD: Comply with all required actions and compliance times specified in, and in accordance with, EASA AD 2024–0022, dated January 23, 2024 (EASA AD 2024–0022).

(h) Exceptions to EASA AD 2024–0022

(1) Where EASA AD 2024–0022 refers to its effective date, this AD requires using the effective date of this AD.

(2) This AD does not adopt the ''Remarks'' section of EASA AD 2024–0022.

(i) Additional AD Provisions

The following provisions also apply to this AD:

(1) *Alternative Methods of Compliance (AMOCs):* The Manager, International Validation Branch, FAA, has the authority to approve AMOCs for this AD, if requested using the procedures found in 14 CFR 39.19. In accordance with 14 CFR 39.19, send your request to your principal inspector or responsible Flight Standards Office, as appropriate. If sending information directly to the manager of the International Validation Branch, mail it to the address identified in paragraph (j) of this AD. Information may be emailed to: *9-AVS-AIR-730-AMOC@faa.gov.* Before using any approved AMOC, notify your appropriate principal inspector, or lacking a principal inspector, the manager of the responsible Flight Standards Office.

(2) *Contacting the Manufacturer:* For any requirement in this AD to obtain instructions from a manufacturer, the instructions must be accomplished using a method approved by the Manager, International Validation Branch, FAA; or EASA; or Airbus SAS's EASA Design Organization Approval (DOA). If approved by the DOA, the approval must include the DOA-authorized signature.

(3) *Required for Compliance (RC):* Except as required by paragraph (i)(2) of this AD, if any material contains procedures or tests that are identified as RC, those procedures and tests must be done to comply with this AD; any procedures or tests that are not identified as RC are recommended. Those procedures and tests that are not identified as RC may be deviated from using accepted methods in accordance with the operator's maintenance or inspection program without obtaining approval of an AMOC, provided the procedures and tests identified as RC can be done and the airplane can be put back in an airworthy condition. Any substitutions or changes to procedures or tests identified as RC require approval of an AMOC.

(j) Additional Information

For more information about this AD, contact Timothy Dowling, Aviation Safety Engineer, FAA, 1600 Stewart Avenue, Suite 410, Westbury, NY 11590; phone 206–231–3667; email *Timothy.P.Dowling@faa.gov.*

(k) Material Incorporated by Reference

(1) The Director of the Federal Register approved the incorporation by reference (IBR) of the material listed in this paragraph under 5 U.S.C. 552(a) and 1 CFR part 51.

(2) You must use this material as applicable to do the actions required by this AD, unless this AD specifies otherwise.

(i) European Union Aviation Safety Agency (EASA) AD 2024–0022, dated January 23, 2024.

(ii) [Reserved]

(3) For EASA AD 2024–0022 identified in this AD, contact EASA, Konrad-Adenauer-Ufer 3, 50668 Cologne, Germany; telephone +49 221 8999 000; email *ADs@easa.europa.eu;* website *easa.europa.eu.* You may find this EASA AD on the EASA website at *ad.easa.europa.eu.*

(4) You may view this material at the FAA, Airworthiness Products Section, Operational Safety Branch, 2200 South 216th St., Des Moines, WA. For information on the availability of this material at the FAA, call 206–231–3195.

(5) You may view this material at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations,* or email *fr.inspection@nara.gov.*

Issued on September 19, 2024.

Peter A. White,

Deputy Director, Integrated Certificate Management Division, Aircraft Certification Service.

[FR Doc. 2024–21811 Filed 9–24–24; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA–2024–N–3533]

Microbiology Devices; Reclassification of Antigen, Antibody, and Nucleic Acid-Based Hepatitis B Virus Assay Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed amendment; proposed order; request for comments.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to reclassify qualitative hepatitis B virus (HBV) antigen assays, qualitative HBV antibody assays and quantitative assays that detect anti-HBs (antibodies to HBV surface antigen (HBsAg)), and quantitative HBV nucleic acid-based assays, all of which are postamendments class III devices, into class II (general controls and special controls), subject to premarket notification. FDA is also proposing three new device classification regulations along with the special controls that the Agency believes are necessary to provide a reasonable assurance of safety and effectiveness for each device.

DATES: Either electronic or written comments on the proposed order must be submitted by November 25, 2024. Please see section X of this document for the proposed effective date when the new requirements apply and for the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of November 25, 2024. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal Rulemaking 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–2024–N–3533 for ''Microbiology Devices; Reclassification of Antigen, Antibody, and Nucleic Acid-Based Hepatitis B Virus Assay Devices.'' Received comments, those filed in a timely manner (see **ADDRESSES**), 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 Eastern Time, 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.'' The Agency will review this copy, including the claimed confidential information, in its 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, the plain language summary of the proposed order of not more than 100 words consistent with the ''Providing Accountability Through Transparency Act,'' 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.

FOR FURTHER INFORMATION CONTACT: Maria Ines Garcia, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3104, Silver Spring, MD 20993, 301–796–7017, *Maria.Garcia@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background—Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (general controls and special controls), and class III (general controls and premarket approval).

Section 513(a)(1) of the FD&C Act defines the three classes of devices. Class I devices are those devices for which the general controls of the FD&C Act (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 (21 U.S.C. 351, 352, 360, 360f, 360h, 360i, or 360j) or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness; or those devices for which insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or to establish special controls to provide such assurance, but because the devices are not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and do not present a potential unreasonable risk of illness or injury, are to be regulated by general controls (section 513(a)(1)(A) of the FD&C Act). Class II devices are those devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, and for which there is sufficient information to establish special controls to provide such assurance, including the issue of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions the Agency deems necessary to provide such assurance (section 513(a)(1)(B) of the FD&C Act). Class III devices are those devices for which insufficient information exists to determine that general controls and special controls would provide a reasonable assurance of safety and effectiveness, and are purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury (section 513(a)(1)(C) of the FD&C Act).

Devices that were not in commercial distribution before May 28, 1976 (generally referred to as ''postamendments devices'') are automatically classified by section 513(f)(1) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless, and until: (1) FDA reclassifies the device into class I or II, or (2) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of the premarket notification procedures in section 510(k) of the FD&C Act and part 807, subpart E (21 CFR part 807, subpart E) of FDA's regulations.

A postamendments device that has been initially classified in class III under section 513(f)(1) of the FD&C Act may be reclassified into class I or class II under section 513(f)(3) of the FD&C Act. Section 513(f)(3) of the FD&C Act provides that FDA, acting by administrative order, can reclassify the device into class I or class II on its own initiative, or in response to a petition from the manufacturer or importer of the device. To change the classification of the device, the proposed new class must have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

FDA relies upon ''valid scientific evidence'', as defined in section 513(a)(3) of the FD&C Act and 21 CFR 860.7(c)(2), in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the ''valid scientific evidence'' upon which the Agency relies must be publicly available (see section 520(c) of the FD&C Act).

Publicly available information excludes trade secret and/or confidential commercial information, *e.g.,* the contents of a pending premarket approval application (PMA) (see section 520(c) of the FD&C Act).

In accordance with section 513(f)(3) of the FD&C Act, FDA is issuing this proposed order to reclassify qualitative HBV antigen assays intended for qualitative detection of HBV antigens as an aid in the diagnosis of acute or chronic HBV infection in specific populations, HBV antibody assays (including qualitative and quantitative anti-HBs) intended for use in the detection of antibodies to HBV, and quantitative HBV nucleic acid-based assays intended for use in the detection of HBV nucleic acid in specimens from individuals with antibody evidence of HBV infection, all of which are postamendments class III devices, into class II (general controls and special controls) subject to premarket notification, under three new device classification regulations with the names ''Qualitative Hepatitis B Virus Antigen Assays,'' ''Hepatitis B Virus Antibody Assays,'' and ''Hepatitis B Virus Nucleic Acid-Based Assays.'' FDA believes the standard in section 513(a)(1)(B) of the FD&C Act is met as there is sufficient information to establish special controls, which, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of these devices.[1]

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. FDA has determined that premarket notification is necessary to provide a reasonable assurance of the safety and effectiveness of HBV antigen assays, HBV antibody assays, and HBV nucleic acid-based assays for their intended uses, therefore, the Agency does not intend to exempt these proposed class II devices from the requirement for premarket notification (510(k)) submission as provided under section 510(m) of the FD&C Act. If this proposed order is finalized, persons who intend to market this type of device must submit to FDA a premarket notification under section 510(k) of the FD&C Act prior to marketing the device.

II. Regulatory History of the Devices

Under section 513(f)(1) of the FD&C Act, qualitative HBV antigen assays, HBV antibody assays (including qualitative and quantitative anti-HBs), and quantitative HBV nucleic acid-based assays are automatically classified into class III because they were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, and have not been found substantially equivalent to a device placed in commercial distribution after May 28, 1976, which was subsequently classified or reclassified into class II or class I. Therefore, they are subject to PMA requirements under section 515 of the FD&C Act (21 U.S.C. 360e). Qualitative HBV antigen assays and HBV antibody assays (including qualitative and quantitative anti-HBs) are prescription devices and assigned product code LOM. Quantitative HBV nucleic acid-based assays are prescription devices and assigned product code MKT.

A. Qualitative HBV Antigen Assays

The first proposed device reclassification action applies to qualitative HBV antigen assay devices that are prescription in vitro diagnostic devices intended for qualitative detection of HBV antigens as an aid in the diagnosis of acute or chronic HBV infection in specific populations. On February 8, 2001, FDA approved its first HBV antigen assay (DiaSorin's ETI–EBK PLUS) for use in the qualitative detection of hepatitis Be antigen (HBeAg) in human serum or plasma (ethylenediaminetetraacetic acid (EDTA), citrate, or heparin) as indicative of a laboratory diagnosis of HBV infection through its PMA process under section 515 of the FD&C Act. On June 1, 2001, FDA approved its first HBV surface antigen (HBsAg) assay (Roche Elecsys HBsAg Immunoassay, Elecsys HBsAg Confirmatory, and Precicontrol HBsAg) for the qualitative detection of HBsAg in human serum or plasma (heparin, EDTA, sodium citrate) in adult pregnant and non-pregnant individuals. In a May 22, 2002, **Federal Register** notice (67 FR 36009), FDA announced the approval order and the availability of the Summary of Safety and Effectiveness Data (SSED) for these devices. Since the first approval order for an HBV antigen assay issued on February 8, 2001, FDA has approved 16 additional original PMAs for qualitative HBV antigen assays that are prescription devices intended for the detection of HBV antigens. These assays are intended as an aid in the diagnosis of acute or chronic HBV infection in conjunction with clinical findings and other diagnostic procedures (*e.g.,* HBV serology and antigen testing, liver function, etc.). These assays are not intended for use in screening of blood, plasma, cells, or tissue donors.

A review of the medical device reporting (MDR) databases indicates that there were 625 reported events for qualitative HBV antigen assays as of June 2024. Of these reported events, a significant majority of these were determined to be of no known impact or consequence to the patient. Events reported included false reactive results, false non-reactive results, incorrect or inadequate assay results, incorrect/inadequate/imprecise readings, improper or incorrect procedure or method, device operates differently than expected, and adverse event without identified device or use problems. Where incorrect results were obtained, it was not clear what the correct result should have been. As of June 2024, there have been no class III recalls, six class II recalls, and no class I recalls[2] involving qualitative HBV antigen assays. The class II recalls occurred since 2006 due to defective caps, device design, no marketing application, signal for reactive results, and biased results for biotin concentrations that were lower than indicated. No patient harm was identified. These facts, coupled with the low number of reported events that caused patient harm, indicate a good safety record for this device class. These recall events reflect the risks to health identified in section V below, and FDA believes the special controls proposed herein, in addition to general controls, can effectively mitigate the risks identified in these recalls.

B. HBV Antibody Assays (Including Qualitative and Quantitative Anti-HBs)

The second type of devices this proposed reclassification order applies to are qualitative HBV antibody assays and quantitative anti-HBs assays that are prescription in vitro diagnostic devices intended for use in the detection of antibodies to HBV. These devices are intended to aid in the diagnosis of HBV infection in persons with signs and symptoms of hepatitis and in persons at risk for HBV infection. On September 29, 2000, FDA approved its first qualitative HBV antibody assay (Ortho-Clinical Diagnostics, Inc.'s Vitros

[1] FDA notes that the ''ACTION'' caption for this proposed order is styled as ''Proposed amendment; proposed order,'' rather than ''Proposed order.'' Beginning in December 2019, this editorial change was made to indicate that the document ''amends'' the Code of Federal Regulations. The change was made in accordance with the Office of the Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

[2] Class I, II, and III recalls are defined in 21 CFR 7.3(m).

Immunodiagnostic Products: Anti-HBS Reagent Pack/Anti-HBS Calibrators) for the qualitative in vitro determination of total antibody to hepatitis B surface antigen (anti-HBs) in human serum as an aid in determining susceptibility to HBV infection for individuals prior to or following HBV vaccination, or where vaccination status is unknown, and for use with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection, through its PMA process under section 515 of the FD&C Act. In a March 12, 2001, **Federal Register** notice (66 FR 14390), FDA announced the approval order and the availability of the SSED for this device. On July 22, 2002, FDA approved its first quantitative Anti-HBs (Siemens Healthcare Diagnostics Products Ltd.'s Immulite 2000 XPI Anti-HBs) for the quantitative measurement of total antibodies to the hepatitis B surface antigen (anti-HBs) in human serum and plasma (heparinized or EDTA) as an aid in the determination of susceptibility to HBV infection for individuals prior to or following HBV vaccination, or where vaccination status is unknown, or for use with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection, through its PMA process under section 515 of the FD&C Act.

Since the first approval order of a qualitative HBV antibody assay on September 29, 2000, FDA has approved 31 additional original PMAs for qualitative HBV antibody assays for the detection of antibodies to HBV. FDA has also approved six assays for quantitative anti-HBs detection. Qualitative HBV antibody assays and quantitative anti-HBs assays are intended to aid in the diagnosis of HBV infection in persons with signs and symptoms of hepatitis and in persons at risk for HBV infection in conjunction with clinical findings and other diagnostic procedures (*e.g.,* HBV serology and antigen testing, liver function, etc.). These assays are not intended for use in screening of blood, plasma, cells, or tissue donors.

A review of the MDR databases indicates that there were 1,107 reported events for HBV antibody assays between years 2001 and June 2024. Of these reported events, a significant majority of these were of no known impact to the patient, and only four resulted in impact to patients such as misdiagnosis or viral infection. Events reported included adverse events without identified device or use problem, disconnection/low assay results, false non-reactive results, false reactive results, false high assay results (for example, the first assay result had a low signal to cutoff (s/co) value and repeat testing produced a higher s/co value), incorrect assay results, inadequate assay results, and low assay results (for example, the first assay result was in the equivocal zone, repeat testing produced a non-reactive result, and testing with an alternate device produced a reactive result). In numerous cases, it was not possible to determine what the correct result should have been (further testing was not performed, insufficient sample volume, different assays were used). As of June 2024, FDA is aware of 4 class III recalls, 12 class II recalls, and no class I recalls for these devices. The class II recalls occurred in 2007, 2008, 2009, 2011, 2012, 2013, 2014, 2018, and 2019, and were related to issues such as false reactive results, false high assay results, defective caps, and errors in labeling, packaging, or software. No patient harm has been identified. These facts, coupled with the low number of reported events that impacted the patient, indicate a good safety record for this device class. These recall events reflect the risks to health identified in section V below, and FDA believes the special controls proposed herein, in addition to general controls, can effectively mitigate the risks identified in these recalls.

C. Quantitative HBV Nucleic Acid-Based Assays

Finally, the third type of device this proposed reclassification order applies to are quantitative HBV nucleic acid-based assay devices for use as a prescription in vitro diagnostic device intended for use in the detection of HBV nucleic acid in specimens from individuals with antibody evidence of HBV infection. On September 4, 2008, FDA approved its first quantitative HBV nucleic assay (Roche Molecular Systems, Inc.'s COBAS TaqMan HBV Test For Use With The High Pure System), an in vitro nucleic acid amplification assay for the quantitation of HBV deoxyribonucleic acid (DNA) in human serum or plasma (EDTA) intended for use as an aid in the management of patients with chronic HBV infection undergoing antiviral therapy, through its PMA process under section 515 of the FD&C Act.

Since the first approval order, FDA has approved four additional original PMAs for quantitative HBV nucleic acid-based assays for the quantitative detection of HBV DNA. The detection of HBV DNA is used for management of patients undergoing antiviral therapy for assessing response to treatment and not as a diagnostic for HBV infection.

The following section provides examples of the different technologies used. The different technologies begin with specimen lysis and HBV DNA through hybridization with magnetic particles. The differences in the technologies occur with the method of amplification:

- In one technology, the target HBV DNA sequence is amplified. The presence of HBV amplification products is detected by measuring the fluorescence of the HBV probe that binds to the target. Similarly, the presence of the internal control amplification product is detected. In the absence of HBV or internal control target sequences, probe fluorescence is quenched. In the presence of HBV or internal control target, the HBV or internal control probes bind to their target.
- In another technology, target amplification occurs via transcription-based nucleic acid amplification by fluorescent labeled probes (torches). More torches hybridize when more amplicon is present creating a higher fluorescent signal. The time taken for the fluorescent signal to reach a threshold proportional to the starting HBV DNA concentration is measured in relation to internal controls.

A review of the MDR databases indicates that as of June 2024 there were 13 reported events for nucleic acid-based HBV DNA assays since the first reported event in 2009. MDRs were for the following reasons: (1) incorrect, inadequate, or imprecise result or readings; (2) high readings; and (3) non-reproducible results. Of these, two had no known impact or consequence to the patient and two occurred when the patient had no signs, symptoms, or conditions. As of June 2024, FDA is aware of one class III recall, five class II recalls, and no class I recalls for these devices. The class II recalls occurred between 2005 and 2022 and were related to issues such as misquantitation of high results for negative samples (carryover from a high positive sample tested adjacent to a negative sample may produce an incorrect positive result), liquid level detection of reagent cassette, under filled and over filled enzyme reagent vials in assay kits, software, and low level of recombinant HBV DNA found in one lot of reagent. These facts, coupled with the low number of reported events that impacted the patient, indicate a good safety record for this device class. These recall events reflect the risks to health identified in section V below, and FDA believes the special controls proposed herein, in addition to general controls, can effectively mitigate the risks identified in these recalls.

III. Device Description

The HBV assays that are the subject of this proposed order are postamendments prescription in vitro diagnostic devices classified into class III under section 513(f)(1) of the FD&C Act.

A. Qualitative HBV Antigen Assays

A qualitative HBV antigen assay is a prescription in vitro diagnostic device intended for use in the qualitative detection of HBV antigens and for use as an aid in the diagnosis of HBV infection in specific populations. HBV antigen assays aid in the diagnosis of acute or chronic HBV infection. HBV antigen assays typically detect the presence of Hepatitis B surface antigen (HBsAg) or Hepatitis B e antigen (HBeAg). HBV antigens (HBsAg and HBeAg), when present in samples, bind to anti-HBs or anti-HBe antibodies to form a complex that is bound to a solid phase (*e.g.,* microparticles, microtiter plate or other technology). Detection of the complexes can be performed using different methods which measure the presence/absence of anti-HBs or anti-HBe antibodies in the sample.

Diagnosis of HBV infection should not be established based on a single assay result but should be determined in conjunction with clinical findings and other diagnostic procedures (*e.g.,* HBV serology and antigen testing, liver function, etc.). These assays are not intended for use in screening of blood, plasma, cells, or tissue donors.

B. HBV Antibody Assays (Including Qualitative and Quantitative Anti-HBs)

A qualitative HBV antibody assay is a prescription in vitro diagnostic device intended for use in the qualitative detection of antibodies to HBV and for use as an aid in the diagnosis of HBV infection in specific populations. HBV antibody assays aid in the diagnosis of HBV infection in persons with signs and symptoms of hepatitis and in persons at risk for HBV infection. Antibody assays typically detect the presence of antibodies to HBsAg (anti-HBs), Hepatitis B core antigen (anti-HBc), or HBeAg (anti-HBe). Diagnosis of HBV infection should not be established based on a single assay result, but should be determined in conjunction with clinical findings and other diagnostic procedures (*e.g.,* HBV serology and antigen testing, liver function, etc.). These assays are not intended for use in screening of blood, plasma, cells, or tissue donors.

A quantitative assay that detects anti-HBs (antibodies to HBV surface antigen (HBsAg)) is a prescription in vitro diagnostic device that is intended for quantitative use to aid in the diagnosis of HBV infection in persons with signs and symptoms of hepatitis and in persons at risk for HBV infection. Detection of anti-HBs indicates a present or past infection with HBV and can be used in conjunction with clinical findings such as other HBV serological markers (detection of other HBV antigens and antibodies to HBV) for diagnosis of HBV infection. Anti-HBs assay results may be used as an aid in the determination of susceptibility to HBV infection in individuals prior to vaccination or when vaccination status is unknown.

In some device designs, HBV antibodies, when present in the sample, bind to HBV antigens to form a complex that is bound to a solid phase (*e.g.,* microparticles, microtiter plate, or other technology). Detection of complexes can be performed using different methods that measure the presence/absence of HBV antibodies in the sample.

C. Quantitative HBV Nucleic Acid-Based Assays

A quantitative HBV nucleic acid-based assay is a prescription in vitro diagnostic device intended for use in the detection of HBV nucleic acid in specimens from individuals with antibody evidence of HBV infection. In these devices, the detection of HBV nucleic acid is used for management of patients undergoing antiviral therapy for assessing response to treatment and NOT as a diagnostic for HBV infection.

FDA is proposing to reclassify qualitative HBV antigen, HBV antibody assays (including qualitative and quantitative anti-HBs), and quantitative HBV nucleic acid-based assays from class III (general controls and premarket approval) to class II (general controls and special controls) and to establish new names for the device types that will be within the classification regulations. FDA proposes to revise 21 CFR part 866 to create three new device classification regulations with the names ''Qualitative Hepatitis B Virus Antigen Assays,'' ''Hepatitis B Virus Antibody Assays,'' and ''Hepatitis B Virus Nucleic Acid-Based Assays.'' FDA believes that these names and proposed identification language most accurately describe these devices.

- A Qualitative Hepatitis B Virus (HBV) Antigen Assay is tentatively identified as an in vitro diagnostic device intended for prescription use for qualitative use with human serum, plasma, or other matrices that aids in the diagnosis of chronic or acute HBV infection. HBV surface antigen (HBsAg) is also used for screening of HBV infection in pregnant women to identify neonates who are at risk of acquiring hepatitis B during perinatal period. The assay is not intended for screening of blood, plasma, cells, or tissue donors.
- A Hepatitis B Virus (HBV) Antibody Assay is tentatively identified as an in vitro diagnostic device intended for prescription use in the detection of antibodies to HBV in human serum and plasma, or other matrices, and or as an aid in the diagnosis of HBV infection in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis B infection. In addition, anti-HBc IgM (IgM antibodies to core antigen) assay is indicative of recent HBV infection. Anti-HBs (antibodies to surface antigen) assay results may be used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or when vaccination status is unknown. The assay is not intended for screening of blood, plasma, cells, or tissue donors. The assay is intended as an aid in diagnosis in conjunction with clinical findings and other diagnostic procedures.
- A Hepatitis B Virus (HBV) Nucleic Acid-Based Assay is tentatively identified as an in vitro diagnostic device intended for prescription use in the detection of HBV nucleic acid in specimens from individuals with antibody evidence of HBV infection. In these devices, the detection of HBV nucleic acid is used as an aid in the management of HBV-infected individuals. The assay is intended for use with human serum or plasma (and other matrices as applicable) from individuals with HBV. The assay is not intended for use as a donor screening assay for the presence of HBV nucleic acids in blood, blood products, plasma, cells, or tissue donors.

Based upon our review experience and consistent with the FD&C Act and FDA's regulations in 21 CFR 860.134, FDA believes that these devices should be reclassified from class III into class II with special controls because there is sufficient information to establish special controls that, along with general controls, can provide reasonable assurance of the devices' safety and effectiveness.

IV. Proposed Reclassification and Summary of Reasons for Reclassification

FDA is proposing to reclassify the HBV assays that are the subject of this proposed order. On September 7, 2023, the Microbiology Devices Panel (Panel) of the Medical Devices Advisory Committee convened to discuss and make recommendations regarding the

reclassification of HBV assays from class III (general controls and premarket approval) to class II (general controls and special controls) (*https://www.fda.gov/media/173609/download*). Panel members unanimously agreed that special controls, in addition to general controls, are necessary and sufficient to mitigate the risks to health of patients presented by these devices and to provide reasonable assurance of the safety and effectiveness of these devices (Refs. 1 and 2). The Panel agreed with FDA-identified risks and identified additional risk(s) and benefit(s) to include in the overall risk assessment. The Panel also discussed potential mitigation measure(s)/control(s) FDA should consider for each of the identified risks and recommended that, as part of any reclassification, the expected performance for these devices should remain the same. Notably, the performance of approved HBV antigen assays has generally been at least 97 percent sensitivity and 99 percent specificity. For approved anti-HBs, anti-Hbe, and anti-HBc total assays the sensitivity has generally been at least 95 percent, for approved anti-HBc IgM assays the sensitivity has been at least 86 percent, and for all HBV approved antibody assays the specificity has generally been above 97 percent.

FDA believes that at this time, sufficient data and information exist such that the risks identified in section V below can be mitigated by establishing special controls, and that these special controls, together with general controls, are necessary to provide a reasonable assurance of the safety and effectiveness of these HBV assays and therefore proposes these devices to be reclassified from class III (general controls and premarket approval) to class II (general controls and special controls). In accordance with section 513(f)(3) of the FD&C Act and 21 CFR part 860, subpart C, FDA is proposing to reclassify qualitative HBV antigen assays, HBV antibody assays (including qualitative and quantitative anti-HBs), and quantitative HBV nucleic acid-based assays from class III into class II, subject to premarket notification (510(k)) requirements. FDA believes that there is sufficient information available to FDA through FDA's accumulated experience with these devices from reviewing the PMAs for these HBV assays, and the Panel considerations and recommendations regarding the proposed special controls that FDA believes would effectively mitigate the risks to health identified in section V. Absent the special controls identified in this proposed order, general controls applicable to the devices are insufficient to provide reasonable assurance of the safety and effectiveness of the devices. FDA expects that the reclassification of these devices would enable more manufacturers to develop these assays such that patients would benefit from increased access to safe and effective tests.

FDA is proposing to create three separate classification regulations for HBV assays that will be reclassified from class III to class II. HBV assays are prescription in vitro diagnostic devices, and under this proposed order, if finalized, these devices will be identified as prescription in vitro diagnostic devices. As such, the devices must satisfy prescription labeling requirements for in vitro diagnostic products (see 21 CFR 809.10(a)(4) and (b)(5)(ii)). In this proposed order, if finalized, FDA has identified the special controls under section 513(a)(1)(B) of the FD&C Act that, together with general controls, will provide a reasonable assurance of the safety and effectiveness of these assays.

FDA is also proposing to create a new product code for HBV antibody assays (including qualitative and quantitative anti-HBs) that will be assigned upon any finalization of this proposed order. Qualitative HBV antigen assays will continue to be assigned the product code LOM upon any finalization of this proposed order.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For these HBV assays, FDA has determined that premarket notification is necessary to provide a reasonable assurance of the safety and effectiveness of these devices. Therefore, the Agency does not intend to exempt these proposed class II devices from 510(k) requirements. If this proposed order is finalized, persons who intend to market a new HBV assay will no longer need to have a PMA for these devices but can instead submit to FDA a 510(k) and receive clearance prior to marketing the device. A 510(k) typically results in a shorter premarket review timeline compared to a PMA, which ultimately provides more timely access of these types of devices to patients.

V. Public Health Benefits and Risks to Health

FDA is providing a substantive summary of the valid scientific evidence concerning the public health benefits of the use of HBV assays (see also *https://www.fda.gov/media/171770/download*), and the nature (and if known, the incidence) of the risks of the devices (see further discussion of the special controls being proposed to mitigate these risks in section VII of this proposed order).

HBV infection represents a significant global public health burden. According to the World Health Organization (WHO), in 2019 there were approximately 296 million people chronically infected people worldwide, with 1.5 million new HBV infections each year.[3] It is estimated by the Centers for Disease Control and Prevention (CDC) that chronic HBV infection in the United States affects at least between 580,000 to 1.17 million people with HBV infection in the United States; two-thirds of whom may be unaware of their infection.[4] HBV infection can be asymptomatic, and accordingly, many HBV-infected individuals are unaware of their HBV infection. Approximately 95 percent of adult patients with acute infection, defined as the first 6 months after infection, recover completely, and 5 percent of adults develop chronic HBV.[5] Infants born to women who are HbsAg-positive are at high risk of HBV infection. In absence of treatment, infants infected with HBV have a 90 percent risk of progression to chronic HBV and up to 25 percent of infants who acquire chronic HBV infection will die prematurely from HBV-related hepatocellular carcinoma or cirrhosis.[6] Patients who are tested and become aware that they are HBV infected may modify risk behaviors to prevent transmission to others and can be referred for treatment. Patients with chronic HBV infection have a risk of developing liver damage, liver cancer, or liver failure. They can also spread their infection to others. HBV can be reactivated in patients receiving immunosuppressive therapies, resulting in serious risk of liver failure or liver-associated death (Ref. 3). HBV is a vaccine-preventable liver infection.

With the initiation of the WHO Viral Hepatitis Elimination Plan[7] and the Department of Health and Human Services (HHS) Viral Hepatitis National

[3] *https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.* Accessed on July 12, 2024.

[4] Centers for Disease Control and Prevention—Clinical Overview of Hepatitis B (Available at *https://www.cdc.gov/hepatitis-b/hcp/clinical-overview/index.html*). Accessed on July 12, 2024.

[5] Ibid.

[6] Ibid.

[7] *https://www.who.int/health-topics/hepatitis/elimination-of-hepatitis-by-2030#tab=tab_1.* Accessed on July 12, 2024.

Strategic Plan for the United States,[8] it is important for individuals to know their HBV infected status, to link HBV infected individuals to care, and to eliminate virus transmission. Therefore, diagnosis of patients with HBV infection through devices such as HBV antibody and antigen assays is essential to ensure that patients are linked to the appropriate care. Current CDC HBV Screening and Testing Recommendations include testing of the following groups: all adults 18 and older at least once in their lifetime using a triple panel test, pregnant women during pregnancy, people who are at ongoing risk for exposure, and anyone who requests HBV testing.[9]

FDA considered our accumulated experience with the regulation of these HBV assays, input from the Panel meeting, and postmarket information regarding these HBV assays, *i.e.,* information from FDA's publicly available MDR, Manufacturer and User Facility Device Experience (MAUDE), and Medical Device Recall databases.

These HBV assays provide a benefit to the public health by informing individuals of their HBV infected status, linking HBV infected individuals to appropriate care, and aiding in eliminating virus transmission. Once an individual is tested and diagnosed as HBV infected, HBV nucleic acid testing is performed to inform treatment decisions. While HBV infection is treatable, it is not curable, which means that most people who start HBV antiviral treatment must continue it for life. The goal of current treatment is to suppress the virus and reduce the likelihood of long-term complications and transmission (Refs. 3 and 4). Thus, identifying individuals who are HBV infected, linking them to care, and managing their HBV infection to alleviate development of liver damage, liver cancer, liver failure, and potential HBV transmission would not only greatly impact public health but also go a long way towards helping the United States achieve HBV elimination.

Probable risks to health associated with the use of HBV assays include risks related to the risk of false results (false positives, false negatives, inaccurate low assay results, inaccurate high assay results, false reactive results, or false non-reactive results), failure to correctly interpret assay results, and failure to correctly operate the device. For HBV antigen and antibody assays, false positive results are generally referred to as false reactive results and false negative results are generally referred to as false non-reactive results. False results can lead to uninfected individuals receiving unnecessary further testing and treatment or infected individuals remaining undiagnosed and untreated. Undiagnosed and untreated individuals are likely to experience increases in morbidity and mortality and can spread the infection to others. FDA has identified the following additional specific risks to health associated with each of the HBV assays listed below.

A. Qualitative HBV Antigen Assays

Factors that may cause decreased assay sensitivity and/or an increased rate of false non-reactive results include, but are not limited to, the presence of interfering substances in the sample, acute infection at a stage that is too early for a device to detect the infection, and antigen concentrations that are too low to be detected by the device. Factors that may lead to false reactive results include device contamination from reactive samples, cross-reactivity with other antigens, or misinterpretation of invalid results as reactive.

- *A false reactive assay result for HbeAg.* Incorrectly interpreting the assay results as a reactive assay result or failing to correctly operate the assay causing a false reactive assay result may lead to continued treatment for hepatitis B with antiviral medication when it otherwise would not be indicated. Antiviral medication has risks including toxicity and more rarely allergic reactions. Over time, viral resistance in patients who are co-infected but undiagnosed with other viruses that are treated with the same antiviral medication, such as HIV, can lead to viral resistance.
- *A false reactive assay result for HbsAg.* Incorrectly interpreting the assay results as a reactive assay result or failing to correctly operate the assay causing a false reactive assay result may contribute to unnecessary additional testing, potentially delaying diagnosis of alternative causes of liver disease when present and may impact the psychological well-being of the patient. Factors that may increase the rate of false reactive assay reporting include cross-reactivity with antigens from other microorganisms or other disease conditions.
- *A false non-reactive result for HbeAg.* Incorrectly interpreting the assay results as a non-reactive assay result or failing to correctly operate the assay causing a false non-reactive assay result may lead to missing the opportunity for treatment of an HBV infected individual with antiviral medication or premature discontinuation of antiviral treatment when continuation of treatment is otherwise indicated should a clinician be falsely led to determine a patient has seroconverted HbeAg to anti-Hbe. Premature discontinuation of antiviral medication could result in adverse effects on patient health, such as cirrhosis, liver cancer, and liver damage, all of which are known to contribute to patient morbidity and mortality, or may contribute to public health risk by leading to virus transmission.
- *A false non-reactive assay result for HbsAg.* Incorrectly interpreting the assay results as a non-reactive assay result or failing to correctly operate the assay causing a false non-reactive assay result may delay or prevent a patient with HBV infection from being identified and linked to care. Missed identification of patients with chronic HBV infection could lead to adverse effects on patient health such as cirrhosis, liver cancer, and liver damage, all of which are known to contribute to patient morbidity and mortality. A false non-reactive HbsAg assay incorrectly interpreted as non-reactive also may contribute to public health risk by leading to virus transmission.

B. HBV Antibody Assays (Including Qualitative and Quantitative Anti-HBs)

Factors that may cause decreased assay sensitivity and/or an increased rate of false non-reactive results include, but are not limited to, the presence of interfering substances in the sample, acute infection at a stage that is too early for a device to detect the infection, and antibody concentrations that are too low to be detected by the device. They also can be caused by misinterpretation of invalid results as non-reactive. Factors that may lead to false reactive results include device contamination from reactive samples, cross-reactivity with other antibodies, or misinterpretation of invalid results as reactive.

- *A false reactive assay result for anti-HBs and anti-HBc.* Incorrectly interpreting the assay results as a reactive assay result or failing to correctly operate the assay causing a false reactive assay result may lead to improper patient management. A false reactive antibody assay result could result in the unnecessary continuation of antiviral treatment. Antiviral medication has risks including toxicity and more rarely allergic reactions. Over time, viral resistance in patients who are co-infected but undiagnosed with other viruses that are treated with the same antiviral medication, such as HIV, can

[8] *https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf.* Accessed on July 12, 2024.

[9] *https://www.cdc.gov/hepatitis/hbv/index.htm.* Accessed on July 12, 2024.

lead to viral resistance. Consequently, repeatedly false reactive results have the potential to lead to inappropriate patient management decisions.

- *A false reactive assay result for anti-HBs.* Incorrectly interpreting the assay results as a reactive assay result or failing to correctly operate the assay causing a false reactive assay result when the device is used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown may cause a patient to be considered previously exposed and therefore immune to HBV or that the patient was successfully vaccinated. A false reactive result may cause the patient to not receive a vaccine, vaccine booster, hyperimmune globulin, and would be at higher risk of infection if exposed to HBV.
- *A false reactive assay result for anti-Hbe.* Incorrectly interpreting the assay results as a reactive assay result, or failing to correctly operate the assay causing a false reactive assay result may lead to missing the opportunity for treatment of HBV infection with antiviral medications in a subset of individuals for whom treatment would otherwise be indicated, or premature discontinuation of antiviral treatment when continuation of treatment is otherwise indicated should a clinician be falsely led to determine a patient has seroconverted HbeAg to anti-Hbe. Premature discontinuation of antiviral medication could result in adverse effects on patient health such as cirrhosis, liver cancer, and liver damage, all of which are known to contribute to patient morbidity and mortality, or may contribute to public health risk by leading to inadvertent transmission of virus by an infected individual.
- *A false non-reactive assay result for anti-HBc.* When the device is used as an aid in the diagnosis of HBV infection in patients with symptoms of hepatitis or who may be at risk for HBV infection, incorrectly interpreting the assay results as non-reactive assay result, or failing to correctly operate the assay causing a false non-reactive assay result may lead to non-diagnosis or a delay in diagnosis of HBV infection with an associated delay in therapy and potentially increased risk of HBV-related morbidity or mortality. Patients with active infection may unknowingly continue to infect others. False non-reactive results can also lead to unnecessary diagnostic evaluation if alternative etiologies of hepatitis are pursued. False non-reactive assay results may occur if the level of antibody in a specimen is below the limit of detection of the assay.
- *A false non-reactive assay result for anti-HBs.* When the device is used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown, incorrectly interpreting the assay results as a non-reactive assay result or failing to correctly operate the assay causing a false non-reactive assay result may lead to unnecessary repeated vaccination for HBV.
- *A false non-reactive assay result for anti-Hbe.* Incorrectly interpreting the assay results as non-reactive assay result or failing to correctly operate the assay causing a false non-reactive assay result may lead to improper patient management, including continued treatment for HBV with antiviral medication. Antiviral medication has risks including toxicity and more rarely allergic reactions. Over time, viral resistance in patients who are co-infected but undiagnosed with other viruses using the same antiviral medication, such as HIV, can lead to viral resistance.

C. Quantitative HBV Nucleic Acid-Based Assays

Decreased assay sensitivity and/or an increased rate of false negative assay reporting may occur with patient samples that contain different genotypes or rare de novo mutations in HBV genomic regions targeted by the device. In these situations, HBV viral load can transiently decrease and/or become undetectable in samples before the virus enters chronic replication.

- *A false positive or falsely elevated quantitative HBV nucleic acid assay result.* Incorrectly interpreting the assay results as a positive assay result or failing to correctly operate the assay causing a false positive assay result may negatively influence patient management decisions. Such decisions may include the administration or continuation of unnecessary antiviral treatment in patients with chronic HBV infection with its known toxicities and more rarely allergic reactions. Certain patients with falsely elevated HBV nucleic acid assay results may not undergo liver biopsy to investigate other causes of liver disease when the biopsy would otherwise be indicated for certain patients.
- *A false negative or falsely decreased quantitative HBV nucleic acid assay result.* Incorrectly interpreting the assay results as a negative assay result, or failing to correctly operate the assay causing a false negative assay result may negatively influence patient management decisions for patients with chronic HBV infection, including the withholding of treatment, failure to treat, or premature discontinuation of treating HBV infection when antiviral treatment is otherwise indicated or the choice of an inappropriate treatment. This could lead to adverse effects on patient health such as progressive liver disease, cirrhosis and/or hepatocellular carcinoma, and other cancers. Patients with active HBV replication also risk spreading the virus to others. Certain patients with falsely low HBV nucleic acid assay results may undergo liver biopsy to investigate other causes of liver disease.

VI. Summary of Data Upon Which the Reclassification Is Based

The safety and effectiveness of these device types has become well established since the initial approval of the first qualitative HBV antibody assay in 2000, the first HBV antigen assay in 2001, and the first quantitative HBV nucleic acid-based assay in 2008. FDA has considered and analyzed the following information: (1) accumulated experience regulating these HBV assays, (2) input from the Panel meeting, and (3) postmarket information regarding HBV assays, *i.e.,* information from FDA's publicly available MDR, MAUDE, and Medical Device Recall databases. The available evidence demonstrates that there are public health benefits derived from the use of HBV assays indicated for use to aid in diagnosis of HBV infection and/or for use to aid in the management of HBV infected patients, or as an aid in the determination of susceptibility to HBV infection (anti-HBs). In addition, the nature of the associated risks to health are known, and special controls can be established to sufficiently mitigate these risks.

Based on our review of the information described above, FDA has determined that special controls, in addition to general controls, are necessary to provide a reasonable assurance of safety and effectiveness for HBV assays, and that sufficient information exists to establish such special controls. Therefore, FDA, on its own initiative, is proposing to reclassify these postamendments devices from class III (general controls and premarket approval) into class II (general controls and special controls), subject to premarket notification (510(k)) requirements.

VII. Proposed Special Controls

FDA believes that these devices can be classified into class II with the establishment of special controls. FDA believes that the following proposed special controls would mitigate each of

the risks to health described in section V and that these special controls, in addition to general controls, would provide a reasonable assurance of safety and effectiveness for HBV assays. Tables 1 through 3 below demonstrate how FDA believes each risk to health described in section V would be mitigated by the proposed special controls for each device type.

A. Qualitative HBV Antigen Assays

The risk of inaccurate interpretation of assay results can be mitigated by special controls requiring certain labeling, including providing clearly stated warnings and limitations and information on principles of operation and procedures in performing the assay.

Risks associated with false results (*e.g.,* false non-reactive and false reactive assay results) and with the failure to correctly operate the device can be mitigated through a combination of special controls, including certain labeling requirements, certain design verification and validation information, and performance studies. Examples of verification and validation information to be included in the design of the device include documentation of performance specifications including analytical and clinical performance criteria. In addition, design verification and validation activities must include documentation of a complete device description, critical reagents, risk analysis strategies, lot release criteria, stability studies, and protocols. Required statements in labeling can aid in mitigating the failure of the device to perform as indicated, for example including a statement that use of the assay with specimen types other than those specifically identified for use with this device may cause inaccurate assay results. Special controls requiring additional labeling to provide a brief summary of the instructions for use can also mitigate these risks.

TABLE 1—RISKS TO HEALTH AND MITIGATION MEASURES FOR QUALITATIVE HBV ANTIGEN ASSAYS

Identified risks to health	Mitigation measures
False reactive/non-reactive assay result	Certain labeling information, including limitations, explanation of procedures, and results interpretation information. Certain design verification and validation information, including certain device description information, risk analysis strategies, lot release criteria, stability studies and protocols, and performance criteria including analytical studies and clinical studies.
Failure to correctly interpret the assay results	Certain labeling information, including warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information, including certain device description information, critical reagent information, risk analysis strategies, lot release criteria, and stability studies and protocols.
Failure to correctly operate the device	Certain labeling information, including warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information, including certain device description, critical reagent information, risk analysis strategies, lot release criteria, and stability studies and protocols.

B. HBV Antibody Assays (Including Qualitative and Quantitative Anti-HBs)

The risk of falsely reactive, non-reactive, elevated, or lowered assay results can be mitigated by special controls requiring certain labeling, including providing clearly stated warnings and limitations and information on principles of operation and procedures in performing the assay.

Risks associated with the failure of the device to perform as indicated (*e.g.,* false non-reactive and false reactive assay results) can be mitigated through a combination of special controls, including certain labeling requirements, certain design verification and validation information, and performance studies. Examples of verification and validation information to be included in the design of the device include documentation of performance specifications including analytical and clinical performance criteria. In addition, design verification and validation activities must include documentation of a complete device description, critical reagents, risk analysis strategies, lot release criteria, stability studies, and protocols. Required statements in labeling can aid in mitigating the failure of the device to perform as indicated; for example, including a statement that use of the assay with specimen types other than those specifically identified for use with this device may cause inaccurate assay results.

TABLE 2—RISKS TO HEALTH AND MITIGATION MEASURES FOR HBV ANTIBODY ASSAYS (INCLUDING QUALITATIVE AND QUANTITATIVE ANTI-HBS)

Identified risks to health	Mitigation measures
False reactive/false non-reactive assay result. In addition, for quantitative assays: Falsely elevated/falsely lowered assay result.	Certain labeling information, including limitations, explanation of procedures, and results interpretation information. Certain design verification and validation information including certain device description information, risk analysis strategies, lot release criteria, stability studies and protocols, and performance criteria including analytical studies and clinical studies.
Failure to correctly interpret the assay results	Certain labeling information, including warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information including certain device description, critical reagent information, risk analysis strategies, lot release criteria, and stability studies and protocols.

TABLE 2—RISKS TO HEALTH AND MITIGATION MEASURES FOR HBV ANTIBODY ASSAYS (INCLUDING QUALITATIVE AND QUANTITATIVE ANTI-HBS)—Continued

Identified risks to health	Mitigation measures
Failure to correctly operate the devices	Certain labeling information, warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information including certain device description, critical reagent information, risk analysis strategies, lot release criteria, and stability studies and protocols.

C. Quantitative HBV Nucleic Acid-Based Assays

The risk of falsely positive, negative, elevated, or lowered assay results can be mitigated by special controls requiring certain labeling, including providing clearly stated warnings and limitations, device description information, and detailed instructions in the device labeling regarding the interpretation of assay results and principles of operation and procedures in performing the assay.

Risks associated with the failure of the device to perform as indicated (*e.g.,* inaccurately low or high results, false negative results, and false positive assay results) can be mitigated through a combination of special controls related to certain labeling requirements, design verification and validation activities, and performance studies. Examples of verification and validation information to be included in the design of the device include documentation of a complete device description, calibrators, critical reagents, traceability, and lot release criteria. In addition, design verification and validation must include documentation of performance specifications, including analytical and clinical performance criteria. Required statements in labeling can aid in mitigating the occurrence of inaccurate results. The risks of false positive/false negative/falsely elevated/falsely lowered results due to decreased assay sensitivity can be mitigated by special controls related to certain labeling, design verification and validation activities, risk analysis strategies, and performance studies.

TABLE 3—RISKS TO HEALTH AND MITIGATION MEASURES FOR QUANTITATIVE HBV NUCLEIC ACID-BASED ASSAYS

Identified risks to health	Mitigation measures
False positive/false negative/falsely elevated/falsely lowered result.	Certain labeling information, including limitations, explanation of procedures, and results interpretation information. Certain design verification and validation information, including certain device description information, risk analysis strategies, lot release criteria, stability studies and protocols, and performance criteria including analytical studies and clinical studies.
Failure to correctly interpret the assay results	Certain labeling information, including warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information, including certain device description, critical reagent information, risk analysis strategies, lot release criteria, and stability studies and protocols.
Failure to correctly operate the device	Certain labeling warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information including certain device description, critical reagent information, risk analysis strategies, lot release criteria, and stability studies and protocols.

If this proposed order is finalized, qualitative HBV antigen assays, HBV antibody assays (including qualitative and quantitative anti-HBs), and quantitative HBV nucleic acid-based assays will be reclassified into class II (general controls and special controls) and would be subject to premarket notification requirements under section 510(k) of the FD&C Act. Firms submitting a 510(k) of the FD&C Act for such devices will be required to comply with the particular mitigation measures set forth in the special controls. FDA believes that adherence to the special controls, in addition to the general controls, is necessary to provide a reasonable assurance of safety and effectiveness of HBV assays.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

While this proposed order contains no new collections of information, it does refer to previously approved FDA collections of information. The previously approved FDA 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 820 have been approved under OMB control number 0910–0073; the collections of information in part 807, subpart E, have been approved under OMB control number 0910–0120; and the collections of information in 21 CFR parts 801 and 809 have been approved under OMB control number 0910–0485.

X. Proposed Effective Date

FDA proposes that any final order based on this proposed order become effective 30 days after the date of its publication in the **Federal Register**.

XI. Codification of Orders

Under section 513(f)(3) of the FD&C Act, FDA may issue final orders to reclassify devices. FDA will continue to codify classifications and

reclassifications in the Code of Federal Regulations (CFR). Changes resulting from final orders will appear in the CFR as newly codified orders. Therefore, under section 513(f)(3) of the FD&C Act, in the proposed order, we are proposing to codify qualitative hepatitis B virus antigen assays in the new § 866.3178, hepatitis B virus antibody assays (including qualitative and quantitative anti-HBs) in the new § 866.3179, and quantitative hepatitis B virus nucleic acid-based assays in the new § 866.3180, under which these HBV assays would be reclassified from class III into class II.

XII. 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. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

*1. Summary Minutes Prepared for the September 7, 2023, Meeting of the Microbiology Devices Panel (available at *https://www.fda.gov/media/173610/download*).

*2. Meeting Transcript Prepared for the September 7, 2023, Meeting of the Microbiology Devices Panel (available at *https://www.fda.gov/media/173609/download*).

3. Terrault, N.A., A.S.F. Lok, B.J. McMahon, et al., ''Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance.'' *Hepatology,* 67(4): 1560–1599, 2018.

4. CDC, ''Clinical Testing and Diagnosis for Hepatitis B,'' *https://www.cdc.gov/hepatitis-b/hcp/diagnosis-testing/index.html.* Accessed July 11, 2024.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 866 be amended as follows:

PART 866—IMMUNOLOGY AND MICROBIOLOGY DEVICES

■ 1. The authority citation for part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360*l,* 371.

■ 2. Add § 866.3178 to subpart D to read as follows:

§ 866.3178 Qualitative hepatitis B virus antigen assays.

(a) *Identification.* A qualitative hepatitis B virus (HBV) antigen assay is identified as an in vitro diagnostic device intended for prescription use for qualitative use with human serum, plasma, or other matrices that aids in the diagnosis of chronic or acute HBV infection. HBV surface antigen (HbsAg) is also used for screening of HBV infection in pregnant women to identify neonates who are at risk of acquiring hepatitis B during perinatal period. The assay is not intended for screening of blood, plasma, cells, or tissue donors.

(b) *Classification.* Class II (special controls). The special controls for this device are:

(1) The labeling required under § 809.10(b) of this chapter must include:

(i) A prominent statement that the assay is not intended for the screening of blood, plasma, cells, or tissue donors.

(ii) A detailed explanation of the principles of operation and procedures for performing the assay.

(iii) A detailed explanation of the interpretation of results.

(iv) Limitations, which must be updated to reflect current clinical practice and disease presentation and management. The limitations must include statements that indicate:

(A) The specimen types for which the device has been cleared, and that use of this assay with specimen types other than those specifically cleared for this device may result in inaccurate assay results.

(B) When appropriate, performance characteristics of the assay have not been established in populations of immunocompromised or immunosuppressed patients or other populations where assay performance may be affected.

(C) Diagnosis of hepatitis B infection should not be established on the basis of a single assay result but should be determined by a licensed healthcare professional in conjunction with the clinical presentation, history, and other diagnostic procedures.

(D) Detection of HBV antigens indicates a current infection with hepatitis B virus but does not differentiate between acute or chronic infection. False reactive HbsAg result may occur for up to 2 weeks after vaccination with HbsAg containing vaccine.

(E) Current methods for the detection of hepatitis B antigens may not detect all potentially infected individuals. A non-reactive assay result does not exclude the possibility of exposure to or infection with hepatitis B virus. A non-reactive assay result in individuals with prior exposure to hepatitis B may be due to but not limited to antigen levels below the detection limit of this assay or lack of antigen reactivity to the antibodies in this assay. HBV mutants lacking the ability to produce antigens have been reported. These may occur as ''escape'' mutants in the presence of anti-HBV antibodies and such patients may be infectious.

(F) Results obtained with this assay may not be used interchangeably with results obtained with a different manufacturer's assay.

(2) Design verification and validation must include the following:

(i) A detailed device description, including all parts that make up the device, ancillary reagents required but not provided, an explanation of the device methodology, design of the capture antibody(ies), external controls, and computational path from collected raw data to reported result (*e.g.,* how collected raw signals are converted into a reported signal and result), as applicable to the detection method and device design.

(ii) For devices with assay calibrators, the design and composition of all primary, secondary, and subsequent quantitation standards used for calibration as well as their traceability to a standardized reference material that FDA has determined is appropriate (*e.g.,* a recognized consensus standard). In addition, analytical testing must be performed following the release of a new lot of the standard material that was used for device clearance or approval, or when there is a transition to a new calibration standard.

(iii) Documentation and characterization (*e.g.,* supplier, determination of identity, purity, and stability) of all critical reagents (including description of the capture antibody(ies)), and protocols for maintaining product integrity throughout its labeled shelf life.

(iv) Risk analysis and management strategies, such as Failure Modes Effects Analysis and/or Hazard Analysis and Critical Control Points summaries and their impact on assay performance.

(v) Final release criteria to be used for manufactured assay lots with appropriate evidence that lots released

at the extremes of the specifications will meet the identified analytical and clinical performance characteristics as well as stability.

(vi) Stability studies for reagents must include documentation of an assessment of real-time stability for multiple reagent lots using the indicated specimen types and must use acceptance criteria that ensure that analytical and clinical performance characteristics are met when stability is assigned based on the extremes of the acceptance range.

(vii) All stability protocols, including acceptance criteria.

(viii) Final release assay results for each lot used in clinical studies.

(ix) Reproducibility study data that includes the testing of three independent production lots.

(x) Detailed documentation of analytical performance studies conducted, as appropriate to the technology, specimen types tested, and intended use of the device, including, the limit of blank (LoB), limit of detection (LoD), cutoff, precision (reproducibility) including lot-to-lot and/or instrument-to-instrument precision, interference, cross reactivity, carryover, hook effect, seroconversion panel testing, matrix equivalency, prominent mutants/variants detection (*e.g.,* for HbsAg), specimen stability, reagent stability, and cross-genotype antigen detection sensitivity, when appropriate.

(xi) Analytical sensitivity of the assay is the same or better than that of other cleared or approved assays.

(xii) For devices with associated software or instrumentation, documentation must include a detailed description of device software, including software applications and hardware-based devices that incorporate software. The detailed description must include documentation of verification, validation, and hazard analysis and risk assessment activities, including an assessment of the impact of threats and vulnerabilities on device functionality and end users/patients as part of cybersecurity review.

(xiii) Detailed documentation and results from a clinical study. Performance must be analyzed relative to an FDA cleared or approved HBV antigen assay or a comparator that FDA has determined is appropriate. This study must be conducted using appropriate patient samples, with an appropriate number of HBV reactive and non-reactive samples in applicable risk and disease categories, and any applicable confirmatory testing. Additional relevant patient groups must be validated as appropriate. The samples must include prospective (sequential) samples for each identified specimen type and, as appropriate, additional characterized clinical samples. Samples must be sourced from geographically diverse areas. This study must be conducted in the appropriate settings by the intended users to demonstrate clinical performance.

■ 3. Add § 866.3179 to subpart D to read as follows:

§ 866.3179 Hepatitis B virus antibody assays (including qualitative and quantitative anti-HBs).

(a) *Identification.* A hepatitis B virus (HBV) antibody assay is identified as an in vitro diagnostic device intended for prescription use in the detection of antibodies to HBV in human serum, plasma, or other matrices, and as a device that aids in the diagnosis of HBV infection in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis B infection. In addition, results from an anti-HBc IgM (IgM antibodies to core antigen) assay indicating the presence of anti-HBc IgM are indicative of recent HBV infection. Anti-HBs (antibodies to surface antigen) assay results may be used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or when vaccination status is unknown. The assay is not intended for screening of blood, plasma, cells, or tissue donors. The assay is intended as an aid in diagnosis in conjunction with clinical findings and other diagnostic procedures.

(b) *Classification.* Class II (special controls). The special controls for this device are:

(1) The labeling required under § 809.10(b) of this chapter must include:

(i) A prominent statement that the assay is not intended for the screening of blood, plasma, cells, or tissue donors.

(ii) A detailed explanation of the principles of operation and procedures for performing the assay.

(iii) A detailed explanation of the interpretation of results.

(iv) Limitations, which must be updated to reflect current clinical practice and disease presentation and management. The limitations must include statements that indicate:

(A) When appropriate, performance characteristics of the assay have not been established in populations of immunocompromised or immunosuppressed patients or other special populations where assay performance may be affected.

(B) Detection of HBV antibodies to a single viral antigen indicates a present or past infection with hepatitis B virus, but does not differentiate between acute, chronic, or resolved infection.

(C) The specimen types for which the device has been cleared, and that use of the assay with specimen types other than those specifically cleared for this device may result in inaccurate assay results.

(D) Diagnosis of hepatitis B infection should not be established on the basis of a single assay result but should be determined by a licensed healthcare professional in conjunction with the clinical presentation, history, and other diagnostic procedures.

(E) A non-reactive assay result may occur early during acute infection, prior to development of a host antibody response to infection, or when analyte levels are below the limit of detection of the assay.

(F) Results obtained with this assay may not be used interchangeably with results obtained with a different manufacturer's assay.

(v) For devices intended for the quantitative detection of HBV antibodies (anti-HBs), in addition to the special controls listed in paragraphs (b)(1) and (2) of this section, labeling required under § 809.10(b) of this chapter must include:

(A) The assay calibrators' traceability to a standardized reference material that FDA has determined is appropriate (*e.g.,* a recognized consensus standard) and the limit of blank (LoB), limit of detection (LoD), limit of quantitation (LoQ), linearity, and precision to define the analytical measuring interval.

(B) Performance results of the analytical sensitivity study testing a standardized reference material that FDA has determined is appropriate (*e.g.,* a recognized consensus standard).

(2) Design verification and validation must include the following:

(i) Detailed device description, including all parts that make up the device, ancillary reagents required but not provided, an explanation of the device methodology, and design of the antigen(s) and capture antibody(ies) sequences, rationale for the selected epitope(s), degree of amino acid sequence conservation of the target, and the design and composition of all primary, secondary and subsequent standards used for calibration.

(ii) Documentation and characterization (*e.g.,* supplier, determination of identity, and stability) of all critical reagents (including description of the antigen(s) and capture antibody(ies)), and protocols for maintaining product integrity throughout its labeled shelf life.

(iii) Risk analysis and management strategies, such as Failure Modes Effects

Analysis and/or Hazard Analysis and Critical Control Points summaries and their impact on assay performance.

(iv) Final release criteria to be used for manufactured assay lots with appropriate evidence that lots released at the extremes of the specifications will meet the identified analytical and clinical performance characteristics as well as stability.

(v) Stability studies for reagents must include documentation of an assessment of real-time stability for multiple reagent lots using the indicated specimen types and must use acceptance criteria that ensure that analytical and clinical performance characteristics are met when stability is assigned based on the extremes of the acceptance range.

(vi) All stability protocols, including acceptance criteria.

(vii) When applicable, analytical sensitivity of the assay is the same or better than that of other cleared or approved assays.

(viii) Analytical performance studies and results for determining the limit of blank (LoB), limit of detection (LoD), cutoff, precision (reproducibility), including lot-to-lot and/or instrument-to-instrument precision, interference, cross reactivity, carryover, hook effect, seroconversion panel testing, matrix equivalency, specimen stability, reagent stability, and cross-genotype antibody detection sensitivity, when appropriate.

(ix) For devices intended for the detection of antibodies for which a standardized reference material (that FDA has determined is appropriate) is available, the analytical sensitivity study and results testing the standardized reference material. Detailed documentation of that study and its results must be provided, including the study protocol, study report, testing results, and all statistical analyses.

(x) For devices with associated software or instrumentation, documentation must include a detailed description of device software, including software applications and hardware-based devices that incorporate software. The detailed description must include documentation of verification, validation, and hazard analysis and risk assessment activities, including an assessment of the impact of threats and vulnerabilities on device functionality and end users/patients as part of cybersecurity review.

(xi) Detailed documentation of clinical performance testing from a clinical study with an appropriate number of HBV reactive and non-reactive samples in applicable risk categories and conducted in the appropriate settings by the intended users. Performance must be analyzed relative to an FDA cleared or approved HBV antibody assay or a comparator that FDA has determined is appropriate. Additional relevant patient groups must be validated as appropriate. The samples must include prospective (sequential) samples for each identified specimen type and, as appropriate, additional characterized clinical samples. Samples must be sourced from geographically diverse areas.

(3) For any HBV antibody assay intended for quantitative detection of anti-HBV antibodies, the following special controls, in addition to those special controls listed in paragraphs (b)(1) and (2) of this section, also apply:

(i) Detailed documentation of the metrological calibration traceability hierarchy to a standardized reference material that FDA has determined is appropriate.

(ii) Detailed documentation of the following analytical performance studies conducted, as appropriate to the technology, specimen types tested, and intended use of the device, including upper and lower limits of quantitation (UloQ and LloQ, respectively), linearity using clinical samples, and an accuracy study using the recognized international standard material.

4. Add § 866.3180 to subpart D to read as follows:

§ 866.3180 Hepatitis B virus nucleic acid-based assays.

(a) *Identification.* A nucleic acid-based hepatitis B virus (HBV) assay is identified as an in vitro diagnostic device intended for prescription use in the detection of HBV nucleic acid in specimens from individuals with antibody evidence of HBV infection. In these devices, the detection of HBV nucleic acid is used as an aid in the management of HBV-infected individuals. The assay is intended for use with human serum or plasma (and other matrices as applicable) from individuals with HBV. The assay is not intended for use as a donor screening assay for the presence of HBV nucleic acids in blood, blood products, plasma, cells, or tissue donors, or as a diagnostic assay to confirm the presence of HBV infection.

(b) *Classification.* Class II (special controls). The special controls for this device are:

(1) Labeling required under § 809.10(b) of this chapter must include:

(i) A prominent statement that the assay is not intended for use as a screening assay for the presence of HBV DNA in blood or blood products, plasma, cells, or tissue donors, or as a diagnostic assay to confirm the presence of HBV infection.

(ii) A detailed explanation of the principles of operation and procedures for performing the assay.

(iii) A detailed explanation of the interpretation of results.

(iv) Limitations, which must be updated to reflect current clinical practice and disease presentation and/or management. These limitations must include statements that indicate:

(A) Management of patients undergoing hepatitis B virus treatment should not be established on the basis of a single assay result but should be determined by a licensed healthcare professional in conjunction with the clinical presentation, history, and other diagnostic procedures, *e.g.,* HBV serologic testing, liver function assays, liver elastography, etc.

(B) The specimen types for which the device has been cleared, and that use of this assay with specimen types other than those specifically cleared for this device may result in inaccurate assay results.

(C) The results obtained with this assay may not be used interchangeably with results obtained with a different manufacturer's assay.

(2) Design verification and validation must include the following:

(i) Detailed device description, including the device components, ancillary reagents required but not provided, and an explanation of the device methodology. Additional information appropriate to the technology must be included such as design of primers and probes, rationale for the selected gene targets, specifications for amplicon size, and degree of nucleic acid sequence conservation.

(ii) For devices with assay calibrators, the design and composition of all primary, secondary, and subsequent quantitation standards used for calibration as well as their traceability to a standardized reference material that FDA has determined is appropriate (*e.g.,* a recognized consensus standard). In addition, analytical testing must be performed following the release of a new lot of the standard material that was used for device clearance or approval, or when there is a transition to a new calibration standard.

(iii) Documentation and characterization (*e.g.,* determination of the identity, supplier, purity, and stability) of all critical reagents (including nucleic acid sequences for primers and probes) and protocols for maintaining product integrity.

(iv) Risk analysis and management strategies demonstrating how risk

control measures are implemented to address device system hazards, such as Failure Modes Effects Analysis and/or Hazard Analysis and Critical Control Points summaries and their impact on assay performance.

(v) Final release criteria to be used for manufactured assay lots with appropriate evidence that lots released at the extremes of the specification will meet the identified analytical and clinical performance characteristics as well as stability.

(vi) Stability studies for reagents must include documentation of an assessment of real-time stability for multiple reagent lots using the indicated specimen types and must use acceptance criteria that ensure that analytical and clinical performance characteristics are met when stability is assigned based on the extremes of the acceptance range.

(vii) All stability protocols, including acceptance criteria.

(viii) Detailed documentation of analytical performance studies conducted as appropriate to the technology, specimen types tested, and intended use of the device, including limit of detection (LoD), linearity, precision, endogenous and exogenous interferences, cross-reactivity, carryover, matrix equivalency, sample and reagents stability, and as applicable, upper and lower limits of quantitation (ULoQ and LLoQ, respectively). Samples selected for use must be from subjects with clinically relevant circulating genotypes in the United States. Cross-reactivity studies must include samples from HBV nucleic acid negative subjects with other viral or non-viral causes of liver disease, including autoimmune hepatitis, alcoholic liver disease, chronic hepatitis C virus (HCV), primary biliary cirrhosis, and nonalcoholic steatohepatitis, when applicable. The effect of each identified nucleic-acid isolation and purification procedure on detection must be evaluated.

(ix) For devices with associated software or instrumentation, documentation must include a detailed description of device software, including software applications and hardware-based devices that incorporate software. The detailed description must include documentation of verification, validation, and hazard analysis and risk assessment activities, including an assessment of the impact of threats and vulnerabilities on device functionality and end users/patients as part of cybersecurity review.

(x) Detailed documentation of performance from a clinical study with a design and number of clinical samples (appropriately statistically powered) that is appropriate for the intended use of the device as well as conducted in the appropriate settings by the intended users. The samples must include prospective (sequential) samples for each claimed specimen type and, as appropriate, additional characterized clinical samples. Samples must be sourced from geographically diverse areas.

Dated: September 20, 2024.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2024–21932 Filed 9–24–24; 8:45 am]

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DEPARTMENT OF STATE

22 CFR Parts 120 and 121

[Public Notice: 12552; DOS–2024–0023]

RIN 1400–AF29

International Traffic in Arms Regulations: Revisions to Definition and Controls Related to Defense Services; Extension of Comment Period

AGENCY: Department of State.

ACTION: Proposed rule; extension of comment period.

SUMMARY: The Department of State is extending the comment period for a proposed rule published July 29, 2024. The original comment period required submission of comments on or before September 27, 2024. In response to requests from the public, the Department extends the comment period through October 15, 2024.

DATES: The comment period for the proposed rule published July 29, 2024, at 89 FR 60980, is extended. Comments should be received on or before October 15, 2024.

ADDRESSES: Interested parties may submit comments by one of the following methods:

- *Email: DDTCPublicComments@state.gov* with the subject line: ''Regulatory Change: Defense Service Definition''.
- *Internet:* At *www.regulations.gov,* search for this notice, by docket number DOS–2024–0023. Additional instructions regarding submission of comments can be found in the document published at 89 FR 60980, July 29, 2024.

FOR FURTHER INFORMATION CONTACT: Sarah Heidema, Director, Office of Defense Trade Controls Policy, Department of State, telephone (202) 663–1282; email *DDTCCustomerService@state.gov.* ATTN: Revisions to Definition and Controls Related to Defense Services.

SUPPLEMENTARY INFORMATION: On July 29, 2024, the Department of State published a proposed rule proposing revisions to the definition of defense service at 22 CFR 120.32 of the International Traffic in Arms Regulations (22 CFR parts 120 through 130) and to the United States Munitions List at 22 CFR 121.1 (89 FR 60980). On the same day, the Department of Commerce published a complementary proposed rule proposing changes to existing restrictions under the Export Administration Regulations (15 CFR parts 730 through 744) on military and intelligence end uses and end users and related controls on certain activities of U.S. persons, as well as the proposed addition of a military-support end-user control (89 FR 60985). In response to requests from the public received by the Department of Commerce, and due to their plan to extend the comment period for their complementary proposed rule for 15 more days, as published via separate notice, the Department of State is similarly extending the comment period for its proposed rule for 15 days.

Stanley L. Brown,

Acting Assistant Secretary, Bureau of Political-Military Affairs, Department of State.

[FR Doc. 2024–22041 Filed 9–23–24; 4:15 pm]

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