FAA–2024–2662; Project Identifier MCAI–2024–00448–T.

(a) Effective Date

This airworthiness directive (AD) is effective October 23, 2025.

(b) Affected ADs

None.

(c) Applicability

This AD applies to The Boeing Company Model 767–300 series airplanes, certificated in any category, that have been modified to a special freighter configuration, in accordance with FAA Supplemental Type Certificate (STC) ST02040SE, and which are listed in paragraph I.A., ''Effectivity,'' of Israel Aerospace Industries Ltd., Service Bulletin 368–34–106, dated August 2024.

(d) Subject

Air Transport Association (ATA) of America Code 34, Navigation.

(e) Unsafe Condition

This AD was prompted by a discovery that certain pitot-static tubing of the first officer's pitot-static system was installed incorrectly in the main and mid equipment center during the airplane conversion from passenger to freighter. The FAA is issuing this AD to address the incorrect installation of the pitot-static tubing of the first officer's pitot-static system. The unsafe condition, if not addressed, may affect the capability to drain water or moisture collected in the first officer pitot-static tubing, and may cause malfunction to the system, leading to an increased flight crew workload and possible loss of control of the airplane.

(f) Compliance

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

(g) Required Actions

Within 36 months after the effective date of this AD, do a visual inspection of the pitot-static rigid tubes, part number (P/N) 233T9110–437 and P/N 233T9110–314, and the flexible hoses, P/N BACH30BC06–0097 and P/N BACH30BC05–0111, at the locations specified in the Accomplishment Instructions of Israel Aerospace Industries Ltd., Service Bulletin 368–34–106, dated August 2024, to determine whether low points exist, and do all applicable related investigative and corrective actions, in accordance with the Accomplishment Instructions of Israel Aerospace Industries Ltd., Service Bulletin 368–34–106, dated August 2024.

(h) 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, send it to the attention of the person identified in paragraph (i) of this AD and email to: *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 the Civil Aviation Authority of Israel (CAAI); or the CAAI's authorized Designee. If approved by the CAAI Designee, the approval must include the Designee's authorized signature.

(i) Additional Information

For more information about this AD, contact Joe Salameh, Aviation Safety Engineer, FAA, 1600 Stewart Avenue, Suite 410, Westbury, NY 11590; telephone: 206–231–3536; email: *Joe.Salameh@faa.gov*.

(j) Material Incorporated by Reference

(1) The Director of the Federal Register approved the incorporation by reference 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) Israel Aerospace Industries Ltd., Service Bulletin 368–34–106, dated August 2024.

(ii) [Reserved]

(3) For Israel Aerospace Industries Ltd. material identified in this AD, contact Israel Aerospace Industries, Ltd., Ben-Gurion International Airport, Israel 70100; telephone 972–39359826; email *tmazor@iai.co.il*.

(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 3, 2025.

Paul R. Bernado,

Acting Director, Compliance & Airworthiness Division, Aircraft Certification Service.

[FR Doc. 2025–18085 Filed 9–17–25; 8:45 am]

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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, Department of Health and Human Services (HHS).

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final order reclassifying qualitative hepatitis B virus (HBV) antigen assays (product code LOM), HBV antibody assays (product code LOM), and quantitative HBV nucleic acid-based assays (product code MKT), all of which are postamendments class III devices, into class II (special controls), subject to premarket notification. FDA is also establishing the special controls that are necessary to provide a reasonable assurance of safety and effectiveness of these device types.

DATES: This order is effective October 20, 2025. See further discussion in Section IV, ''Implementation Strategy.''

FOR FURTHER INFORMATION CONTACT: Bhawna Poonia, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3226, Silver Spring, MD 20993, 240–402–6830, *bhawna.poonia@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 classes of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three classes of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Devices that were not in commercial distribution prior to 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 action taken by FDA (or the Agency). 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 previously marketed devices by means of the procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and our implementing regulations (part 807, subpart E (21 CFR part 807, subpart E)).

A postamendments device that has been initially classified into 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) 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 new class must have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.[1]

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.[2] In general, to be considered in the reclassification process, the ''valid scientific evidence'' upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, *e.g.,* the contents of a pending PMA (see section 520(c) of the FD&C Act (21 U.S.C. 360j(c))).

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the requirements under section 510(k) of the FD&C Act if FDA determines that a premarket notification (510(k)) is not necessary to provide reasonable assurance of the safety and effectiveness of the device type.

On September 25, 2024, FDA published a proposed order[3] in the **Federal Register** to reclassify qualitative HBV antigen assays (product code LOM),[4] qualitative HBV antibody assays and quantitative assays that detect anti-HBs (antibodies to HBV surface antigen (HBsAg)) (product code LOM),[5] and quantitative HBV nucleic acid-based assays (product code MKT) from class III to class II (89 FR 78265, the ''proposed order'').[6] FDA has considered the information available to the Agency, including the deliberations of the Microbiology Devices Panel (the ''Panel'') convened on September 7, 2023, to discuss the proposed reclassification of these devices, and considered comments for that meeting as well as comments received from the public docket on the proposed order (as discussed in Section II of this document), to determine that there is sufficient information to establish special controls to effectively mitigate the risks to health. FDA has also determined that based on this information that the special controls, together with general controls, provide a reasonable assurance of safety and effectiveness when applied to these devices.

Therefore, in accordance with section 513(f)(3) of the FD&C Act, FDA, on its own initiative, is issuing this final order[7] to reclassify qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays[8] from class III (premarket approval) to class II (special controls). Absent the special controls identified in this final order, general controls applicable to these device types are insufficient to provide reasonable assurance of the safety and effectiveness of these devices. FDA expects that the reclassification of these devices will enable more manufacturers to develop these types of devices such that patients will benefit from increased access to safe and effective diagnostics.

For these class II devices, instead of a PMA, manufacturers may submit a premarket notification and obtain FDA clearance of the devices before marketing them. This action will decrease regulatory burden on industry, as manufacturers will no longer have to submit a PMA for these types of devices but can instead submit a 510(k) to the Agency for review prior to marketing their device. A 510(k) typically results in a shorter premarket review timeline compared to a PMA, which ultimately provides patients with more timely access to these types of devices.

This final order is expected to result in decreased regulatory burdens for affected devices moved from class III to class II and is considered deregulatory under Executive Order 14192.

II. Comments on the Proposed Order and FDA Responses

A. Introduction

FDA received more than 25 comments on the proposed order. The comment period on the proposed order closed on November 25, 2024. The majority of the comments received by the close of the comment period came from research, disease and patient advocacy groups, individual medical professionals and an association of health care organizations, patients, and members of the medical device industry. Many commenters provided multiple comments on one or more issues. Comments provided support for the proposed reclassification

[1] See section 513 of the FD&C Act.

[2] *Id.*

[3] The ''ACTION'' caption for this proposed order was styled as ''Proposed amendment; proposed order; request for comments'' 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.

[4] FDA's Center for Devices and Radiological Health (CDRH) uses product codes to help categorize and ensure consistent regulation of medical devices. A product code consists of three characters that are assigned at the time a product code is generated and is unique to a product type. The three characters carry no other significance and are not an abbreviation. See FDA guidance entitled, ''Medical Device Classification Product Codes'' available at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-classification-product-codes-guidance-industry-and-food-and-drug-administration-staff.*

[5] These devices are currently regulated under product code LOM, but upon the finalization of this action they will fall within the newly created product code SEI.

[6] In the proposed order, FDA proposed to reclassify ''Hepatitis B virus antibody assays (including qualitative and quantitative anti-HBs)'' under the classification regulation 21 CFR 866.3179. In this final order, FDA is simplifying the identification of the classification regulation name to ''Hepatitis B virus antibody assays'' and adding further description to the identification language to better describe the devices that fit within this generic device type and are subject to this reclassification order. In addition, in the proposed order, FDA proposed to reclassify qualitative hepatitis B virus antigen assays under new classification regulation 21 CFR 866.3178 and quantitative hepatitis B virus nucleic acid-based assays under new classification regulation 21 CFR 866.3180. However, at the time of publication of this final order, a different regulation has been codified at § 866.3180. Therefore, in this final order, FDA is reclassifying these device types under different sections of the Code of Federal Regulations than was proposed in the proposed order. Specifically, FDA is reclassifying qualitative hepatitis B virus antigen assays under new classification regulation 21 CFR 866.3172, hepatitis B virus antibody assays under new classification regulation 21 CFR 866.3173, and hepatitis B virus nucleic acid-based assays under new classification regulation 21 CFR 866.3174.

[7] FDA notes that the ''ACTION'' caption for this final order is styled as ''Final amendment; final order,'' rather than ''Final 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 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.

[8] We use the phrase ''quantitative HBV nucleic acid-based assays'' to refer to the devices being reclassified in 21 CFR 866.3174 Hepatitis B virus nucleic acid-based assays.

as well as included recommendations for clarity.

We describe and respond to the comments in Section II.B of this document. The order of the comments and our response to them is purely for organizational purposes and does not signify the comment's value or importance of the comment nor the order in which comments were received. Certain comments are grouped together under a single number because the subject matter is similar. Please note that in some cases we separate different issues discussed by the same commenter and designate them as distinct comments for purposes of our responses.

B. Description of Comments and FDA Response

(Comment 1) FDA received numerous comments in favor of the proposed reclassification of 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 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, from class III to class II with special controls. Commenters stated they believe that special controls, along with general controls, could provide reasonable assurance of the safety and effectiveness of these devices. In addition, they believed that the decreased regulatory burden resulting from the reclassification could encourage further development of, and provide patients more timely access to, these devices.

(Response 1) Based on the evidence considered, comments received in response to the proposed order, and the 2023 Panel deliberations (Refs. 1 and 2), FDA agrees with the commenters that reclassification of qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays from class III into class II and that special controls, in addition to general controls, can provide reasonable assurance of the safety and effectiveness of these devices. In addition, FDA expects that the reclassification of these devices would enable more manufacturers to develop them such that patients would benefit from increased access to safe and effective tests.

(Comment 2) Many commenters emphasized the importance of Point of Care (PoC) tests, particularly for settings that do not have access to blood serum testing whether because of cost or patient hesitancy, for testing and treating patients at the same visit and reducing the risk of patients not returning for follow-up, and for increased mobility and portability. Several commenters suggested that FDA should consider a Clinical Laboratory Improvements Amendments of 1988 (CLIA)—waiver designation for hepatitis B testing to make PoC tests available.

(Response 2) These comments are beyond the scope of FDA's reclassification order, which applies only to qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays that have been previously approved by FDA. FDA has not approved any such assays as PoC tests or categorized them as CLIA waived. FDA agrees that PoC tests should increase access to testing and encourages the development of such tests in the future.

(Comment 3) Several comments suggested that FDA set reasonable cutoff values for test sensitivity and specificity, and asserted this would make it feasible for a PoC test to be available in the United States, while limiting false positives and false negatives. Several comments also recommended information be provided, such as sensitivity and specificity benchmark values or a statement to guide clinicians on whether or not reflex testing is warranted, due to the potential for misleading results.

One commenter stated that screening tests should have high sensitivity to reduce the incidence of false negative results. In situations where a hepatitis B PoC test may have lower sensitivity, the commenter further recommended inclusion of a statement that individuals should have lab-based triple panel confirmatory testing that includes testing for HBsAg, hepatitis B surface antibody (anti-HBs), and total antibody to hepatitis B core antigen (total anti-HBc) to definitively determine a person's hepatitis B status.

(Response 3) As discussed in response to comment 2, PoC tests are outside the scope of this reclassification. Moreover, the Panel recommendations from the September 7, 2023, meeting were unanimous that performance expectations should not be compromised or lowered compared with approved tests (Refs. 1 and 2). The proposed special controls for qualitative HBV antigen assays and, when applicable, HBV antibody assays state that analytical sensitivity of the assay is the same or better than that of other cleared or approved assays. FDA has added this special control in § 866.3174(b)(2)(ix) for HBV nucleic acid-based assays because it was inadvertently omitted from the proposed order. FDA continues to believe that the special controls finalized in this administrative order are necessary and sufficient to provide reasonable assurance of safety and effectiveness for the HBV assays that are within the scope of this final order.

The comments regarding providing sensitivity and specificity benchmark values to guide reflex testing and triple panel confirmatory testing are beyond the scope of this reclassification order as they relate to the practice of medicine and current Centers for Disease Control and Prevention (CDC) guidelines (Ref. 3). However, we note that such guidelines are useful to practitioners as they administer these tests and we acknowledged such guidelines in our proposed order.[9]

FDA also notes that the scope of the order is diagnostic devices reviewed by CDRH. Screening tests are not within the scope of the reclassification order as indicated by the identification of the respective classification regulations.

(Comment 4) Several comments encouraged FDA to allow reliable data obtained from approved hepatitis B PoC tests used globally with success for many years when determining the required sample size within the United States.

(Response 4) As discussed in response to comment 2, PoC tests are outside the scope of this reclassification because FDA has not approved qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays as PoC tests. FDA has not specified a sample size requirement as a necessary risk mitigation in the proposed special controls or final special controls included within this final order. Regarding the utilization of data sourced from outside the United States, FDA has regulations on the acceptance of data from clinical investigations conducted outside the United States (OUS) to support marketing applications for devices and recommends that sponsors that include OUS data in their marketing application explain how the OUS data are applicable to the US population and US medical practice.[10]

[9] See 89 FR 78265 at 78271.

[10] See ''Human Subject Protection; Acceptance of Data from Clinical Investigations for Medical Devices'' (83 FR 7366) and FDA guidance entitled ''Acceptance of Clinical Data to Support Medical Device Applications and Submissions Frequently Asked Questions'', available at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked.*

(Comment 5) Some commenters asked for clarification on whether the proposed reclassification is referring to all anti-HBV immunoassays, which would include the rapid serum assays commonly used in the inpatient setting. Commenters stated that it was unclear whether hepatitis B core antibody (HBcAb) Immunoglobulin M (IgM) and Immunoglobulin G (IgG), hepatitis B core antibody total (HBcAb total), and HBe antibody are included in the proposed reclassification.

(Response 5) The identification language in the classification regulation for HBV antibody assays as stated in the proposed order and new § 866.3173 states that an HBV antibody assay is ''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'' (see § 866.3173(a)). This classification regulation covers HBV antibody assay types approved to date and assigned to product code LOM,[11] including serology devices that detect anti-HBc IgM, anti-HBc IgG, anti-HBc total, anti-HBs and anti-HBe. To further clarify which devices are included within the classification, we are simplifying the classification regulation name to ''Hepatitis B virus antibody assays'' and explaining in the identification language that ''results from assays may be qualitative or quantitative, such as quantitative anti-HBs.'' The quantitative HBV antibody assays approved to date are quantitative anti-HBs. A quantitative HBV antibody assay other than for anti-HBs could also potentially fall within this classification regulation, if the device has the same intended use and does not raise different questions of safety and effectiveness.[12]

(Comment 6) One commenter encouraged FDA to continue post approval safety surveillance and consider implementing mandatory reviews by third parties at certain time intervals to ensure the specificity and sensitivity of these assays remain as initially reported.

(Response 6) FDA notes there are various mechanisms in place to monitor the post market safety of devices. FDA maintains the MDR database, MAUDE database, and Medical Device Recall database, which allows for additional post-market surveillance of these devices and helps to ensure continued safety for marketed devices. For example, manufacturers are required to report to FDA information that reasonably suggests that their device may have caused or contributed to a death or serious injury, or has malfunctioned and the device or a similar device that the manufacturer markets would be likely to cause or contribute to a death or serious injury if the malfunction were to recur under section 519(a) of the FD&C Act (21 U.S.C. 360i(a)). Manufacturers also must report to FDA any correction or removal of a device undertaken to reduce a risk to health posed by the device, or to remedy a violation of the FD&C Act caused by the device which may present a risk to health under section 519(g) of the FD&C Act. Additionally, if a device's quality falls below that which it purports or is represented to possess, then it may be deemed to be adulterated under section 501(c) of the FD&C Act (21 U.S.C. 351(c)). In addition, routine or for-cause inspections, which may consider compliance with quality system requirements [13] applicable to the device, allow for appropriate post-market oversight of these devices with respect to inspections. Hence, FDA does not believe that additional postmarket special controls are necessary to provide reasonable assurance of safety and effectiveness for the HBV assays that are within the scope of this final order. The suggestion of mandatory reviews by third parties is outside the scope of this reclassification order.

(Comment 7) One comment stated that there should be clear instructions to inform individuals that hepatitis B testing performed during early infection may not accurately detect hepatitis B and it is critical for these individuals to be retested at the appropriate interval to reduce the likelihood of false negative results and missed diagnoses.

(Response 7) FDA agrees with this comment. The special controls for the HBV antibody assays include labeling limitations that 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'' (see § 866.3173(b)(1)(iv)(E)). Additionally, the special controls for the HBV antigen assays include labeling limitations that state that a ''non-reactive assay result does not exclude the possibility of exposure to or infection with hepatitis B virus'' (see § 866.3172(b)(1)(iv)(E)). Finally, the special controls include labeling limitations that indicate that ''[d]iagnosis 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'' (see § 866.3172(b)(1)(iv)(C); § 866.3173(b)(1)(iv)(D)).

(Comment 8) One comment stated there is significant confusion among clinicians regarding when it is appropriate to order total antibody to hepatitis B core antigen (total anti-HBc, which is a measure of both anti-HBc IgG and anti-HBc IgM) testing and when to order hepatitis B core antibody IgM (anti-HBc IgM) testing and how to interpret the results. The commenter recommended the inclusion of clear instructions that clarify anti-HBc IgM testing align with CDC guidelines. Another comment also recommended clear instructions on when to test for and how to interpret the different types of hepatitis B core antibody tests.

(Response 8) These comments regarding when to conduct total anti-HBc testing or anti-HBc IgM testing based on CDC guidelines and recommendations for clear instructions on testing and interpretation of hepatitis B core antibody tests relate to medical practice guidelines and recommendations provided by professional organizations and are beyond the scope of this reclassification order. However, the special controls for HBV antibody assays include labeling to provide detailed explanation of the interpretation of results and limitations, which must be updated to reflect current clinical practice and disease presentation and management, that address result interpretation (see § 866.3173(b)(1)(iii) and (iv)).

[11] As noted elsewhere in this document, upon the finalization of this action these devices will fall within the newly created product code SEI.

[12] The statutory standard for establishing substantial equivalence is defined in section 513(i) of the FD&C Act and further described in FDA guidance entitled ''The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], available at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k*.

[13] On February 2, 2024, FDA issued a final rule amending the device Quality System Regulation, 21 CFR part 820, to align more closely with internal consensus standards for devices (89 FR 7496). This final rule will take effect on February 2, 2026. Once in effect, this rule will withdraw the majority of the current requirements in part 820 and instead incorporate by reference the 2016 edition of the International Organization for Standardization (ISO) 13485, Medical devices—Quality management systems—Requirements for regulatory purposes, in part 820. As stated in the final rule, the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the current part 820, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the FD&C Act.

(Comment 9) Another comment stated that for all positive PoC test results, there should be clear instructions on the type of testing necessary to confirm an individual's hepatitis B status. The commenter also stated that for negative PoC test results, the individual should be informed of the need for hepatitis B vaccination to prevent infection.

(Response 9) These comments regarding confirmatory testing and medical practice and recommendations provided by professional organizations are beyond the scope of this reclassification order.

(Comment 10) One comment requested that FDA consider expanding the regulation for quantitative HBV nucleic acid-based assays to include diagnostic use (independent of antibody status) for HBV infection in addition to monitoring. The comment stated that detectable HBV DNA is indicative of infection and can be used as a diagnostic marker. In addition, HBV DNA may be detectable sooner after infection than viral antigens and/or antibodies and therefore may enable earlier detection of infection or reactivation of infection.

(Response 10) This comment is beyond the scope of this reclassification order, which applies only to nucleic acid-based HBV DNA tests for patient management that have been previously approved by FDA. FDA has not approved nucleic acid-based HBV DNA tests intended for diagnosis of HBV infection. Thus, this additional intended use is beyond the scope of FDA's reclassification order.

(Comment 11) One commenter noted the special controls for HBV nucleic acid-based assays state that: ''Samples selected for use must be from subjects with clinically relevant circulating genotypes in the United States'' (see § 866.3174(b)(2)(viii)). The commenter requested FDA clarify whether clinical specimens must be used for the analytical studies and whether samples contrived using pre-screened HBV negative clinical specimens containing clinically relevant circulating HBV genotypes in the United States could be used in analytical studies. The commenter suggested that FDA revise the statement to ''Samples selected for use in analytical studies or used to prepare samples for use in analytical studies must be from subjects with clinically relevant circulating genotypes in the United States.''

(Response 11) FDA disagrees that such a clarification is needed. In the past, FDA has generally preferred native clinical samples to provide a reasonable assurance of safety and effectiveness for HBV assays. However, FDA has considered alternative approaches that used contrived samples in specific analytical studies with adequate justification, for example, see the Summary of Safety and Effectiveness Data for P190034 (Ref. 4).

(Comment 12) One commenter supported FDA's proposal to reclassify certain hepatitis B assays from class III to class II and, citing human immunodeficiency virus (HIV), hepatitis and sexually transmitted infections, stated that FDA should continue to partner with the CDC, National Institutes of Health (NIH) and others to support additional research and interdisciplinary collaboration on these issues. The commenter also recommended that FDA and its partners evaluate the impact of this and other reclassifications in the context of other proposed or recently implemented changes, including those changes per FDA's January 31, 2024, announcement [14] that it intended to initiate the reclassification process for most high risk IVDs, the majority of which are infectious disease and companion diagnostic in vitro diagnostic devices.

(Response 12) FDA appreciates these comments. FDA is undertaking this reclassification of certain HBV assays on its own initiative as reflected in the Agency's January 31, 2024, announcement. As warranted, FDA collaborates with other organizations such as CDC and NIH to support cross-cutting issues.

(Comment 13) One commenter recommended that FDA introduce an app that would connect administrators, vaccine manufacturers, public and private vaccine facilities, vaccine recipients, etc. The commenter envisioned that the app would allow individuals to book and schedule online appointments for vaccination and obtain a vaccine certificate and track adverse events following immunization.

(Response 13) This comment is beyond the scope of this reclassification order.

(Comment 14) Several commenters also asked FDA to reclassify quantitative HBsAg assays and asserted these assays will be necessary to predict response and monitor efficacy of new therapies that are now in clinical testing if such therapies are approved. One commenter asked FDA to provide device classification if a rapid device is used in combination with other analytes such as HIV Ab, hepatitis C virus (HCV) Ab, or syphilis testing.

(Response 14) FDA has not approved any quantitative HBsAg test, nor any HBV assay in combination with other analytes such as HIV Ab, HCV Ab, or syphilis testing, thus the comments requesting the reclassification of such devices are beyond the scope of this reclassification order.

III. The Final Order

FDA is adopting its findings under section 513(f)(3) of the FD&C Act, as published in the preamble to the September 25, 2024 proposed order (89 FR 78265). FDA has made some minor revisions in this final order in response to comments received (see Section II). FDA is issuing this final order to reclassify qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays from class III into class II under three new device classification regulations, and to establish special controls by revising 21 CFR part 866 (adding 21 CFR 866.3172, 866.3173, and 866.3174, respectively).

The qualitative HBV antigen assay is assigned the classification regulation name ''Qualitative hepatitis B virus antigen assays'' and it 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. 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.

The HBV antibody assay is assigned the classification regulation name ''Hepatitis B virus antibody assays'' and it 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. Results from assays may be qualitative or quantitative, such as quantitative anti-HBs. 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

[14] CDRH Announces Intent to Initiate the Reclassification Process for Most High Risk IVDs | FDA available at *https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-announces-intent-initiate-reclassification-process-most-high-risk-ivds.*

blood, plasma, cells, or tissue donors. The assay is intended as an aid in diagnosis in conjunction with clinical findings and other diagnostic procedures. The identification for § 866.3173(a)(1) has been revised to provide a more accurate description of the devices in this classification regulation.

The quantitative HBV nucleic acid-based assay is assigned the classification regulation name ''Hepatitis B virus nucleic acid-based assays'' and it 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.

Based on the information discussed in the preamble to the proposed order, the comments received for the proposed order and the Panel meeting, and the 2023 Panel deliberations (Ref. 1 and 2), FDA concludes that special controls, in addition to general controls, provide a reasonable assurance of the safety and effectiveness of qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays. In this final order, the Agency has identified the special controls under section 513(a)(1)(B) of the FD&C Act that, along with general controls, provide a reasonable assurance of the safety and effectiveness of these devices. In this final order, FDA has added the special control at § 866.3174(b)(2)(ix) to require that design verification and validation include analytical sensitivity of the assay that is the same or better than that of other cleared or approved assays because this special control was inadvertently omitted from the proposed order. In addition, FDA has simplified the classification regulation name in § 866.3173 to ''Hepatitis B virus antibody assays'' and also clarified in the identification language which assays fall within the classification regulation. Finally, in this final order, to provide additional clarification and to efficiently implement this order, the Agency has added an implementation strategy in Section IV.

FDA has also created a new product code SEI for HBV antibody assays. Qualitative HBV antigen assays will continue to be assigned the product code LOM. Quantitative HBV nucleic acid-based assays will continue to be assigned the product code MKT.

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.[15] FDA has determined that premarket notification is necessary to provide a reasonable assurance of the safety and effectiveness of qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays. Therefore, these devices are not exempt from premarket notification requirements. Thus, under sections 510(k) and 513(f) of the FD&C Act, persons who intend to market a device in any of these device types must submit to FDA a premarket notification, obtain clearance, and demonstrate compliance with the special controls included in this final order, prior to marketing the device.

Manufacturers may wish to use predetermined change control plans (PCCPs) as a way to implement future modifications to their devices without needing to submit a new 510(k) for each significant change or modification [16] while continuing to provide a reasonable assurance of device safety and effectiveness.[17] FDA reviews a PCCP as part of a marketing submission for a device to ensure the continued safety and effectiveness of the device without necessitating additional marketing submissions for implementing each modification described in the PCCP. When used appropriately, PCCPs authorized by FDA are expected to be least burdensome for manufacturers and FDA.[18]

Under this final order, these qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays are prescription use IVD devices and as such, these assays must satisfy prescription labeling requirements for in vitro diagnostic products (see 21 CFR 809.10(a)(4) and (b)(5)(ii)). These device types would continue to be subject to the submission and device clearance requirements of sections 510(k) and 513 of the FD&C Act and of part 807, subpart E.

IV. Implementation Strategy

This final order is effective 30 days after the date of its publication in the **Federal Register**.

For qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays that have not been offered for sale prior to the effective date of the final order, or for devices that have been legally marketed via PMA before the effective date of this final order but the device is about to be significantly changed or modified per 21 CFR 807.81(a)(3) after the effective date, manufacturers must obtain 510(k) clearance, among other relevant requirements, and demonstrate compliance with the special controls included in this final order, before marketing the new or changed device.

For qualitative HBV antigen assays, HBV antibody assays, and quantitative HBV nucleic acid-based assays that have been offered for sale prior to the effective date of the final order and have prior PMA approval, such devices may continue to be marketed per the previously approved PMA and do not require an additional marketing application. Any future changes to the device would be subject to 510(k) requirements and governed by 21 CFR 807.81(a)(3).

V. 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

[15] In considering whether to exempt class II devices from premarket notification, FDA considers whether premarket notification for the type of device is necessary to provide reasonable assurance of safety and effectiveness of the device. FDA generally considers the factors initially identified in 63 FR 3142 (January 21, 1998) and further explained in FDA guidance ''Procedures for Class II Device Exemptions from Premarket Notification, Guidance for Industry, and CDRH Staff'' to determine whether premarket notification is necessary for class II devices. FDA also considers that even when exempting devices from the 510(k) requirements, these devices would still be subject to certain limitations on exemptions, for example, the general limitations set forth in 21 CFR 866.9.

[16] For the purpose of this final order reference to ''modification'' means a significant change or modification that would generally require a new premarket notification under 21 CFR 807.81(a)(3).

[17] Section 3308 of the Food and Drug Omnibus Reform Act of 2022, Title III of Division FF of the Consolidated Appropriations Act, 2023, Public Law 117–328 (''FDORA''), enacted on December 29, 2022, added section 515C ''Predetermined Change Control Plans for Devices'' to the FD&C Act. Section 515C has provisions regarding predetermined change control plans (PCCPs) for devices requiring premarket approval or premarket notification. Under section 515C, supplemental applications (section 515C(a)) and new premarket notifications (section 515C(b)) are not required for a change to a device that would otherwise require a premarket approval supplement or new premarket notification if the change is consistent with a PCCP approved or cleared by FDA.

[18] Sections 513 and 515 of the FD&C Act. See also, FDA's guidance ''The Least Burdensome Provisions: Concept and Principles | FDA''.

environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This final administrative order establishes special controls that refer to previously approved collections of information found in FDA regulations. These previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). The collections of information in 21 CFR part 820 (Quality System Regulation) have been approved under OMB control number 0910–0073; the collections of information in part 807, subpart E (Premarket Notification Procedures), have been approved under OMB control number 0910–0120; and the collections of information in 21 CFR parts 801 and 809 (Device Labeling) have been approved under OMB control number 0910–0485.

VII. 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, we are codifying in this final order the classification of (i) qualitative hepatitis B virus antigen assays in the new 21 CFR 866.3172; (ii) hepatitis B virus antibody assays in the new 21 CFR 866.3173; and (iii) hepatitis B virus nucleic acid-based assays in the new 21 CFR 866.3174, under which each of these device types are reclassified from class III into class II.

VIII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500, 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. Meeting Transcript Prepared for the September 7, 2023, Meeting of the Microbiology Devices Panel (available at *https://www.fda.gov/media/173609/download*).

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

3. CDC, ''Clinical Testing and Diagnosis for Hepatitis B,'' *https://www.cdc.gov/hepatitis-b/hcp/diagnosis-testing/index.html.* Accessed March 18, 2025.

*4. P190034 Summary of Safety and Effectiveness, available at: *https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190034B.pdf.*

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 *et seq.,* as amended), and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is 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 § 866.3172 to subpart D to read as follows:

§ 866.3172 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 that 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 § 866.3173 to subpart D to read as follows:

§ 866.3173 Hepatitis B virus antibody assays.

(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. Results from assays may be qualitative or quantitative, such as quantitative anti-HBs. 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 that 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 § 866.3174 to subpart D to read as follows:

§ 866.3174 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 HBV 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, 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) Analytical sensitivity of the assay that is the same or better than that of other cleared or approved assays.

(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 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.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

[FR Doc. 2025–18082 Filed 9–17–25; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 1010

[Docket No. FDA–2018–N–3303]

Radiological Health Regulations; Technical Amendments

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; technical amendments.

SUMMARY: The Food and Drug Administration (FDA) is making technical amendments to its radiological health regulations to correct an error. On January 20, 2023, FDA published a final rule entitled ''Radiological Health Regulations; Amendments to Records and Reports for Radiation Emitting Electronic Products; Amendments to Performance Standards for Diagnostic X-ray, Laser, and Ultrasonic Products'' that inadvertently deleted certain existing regulatory text from the Code of Federal Regulations. This action corrects the error by restoring the inadvertently deleted regulatory text. This action is editorial in nature and is intended to ensure accuracy and clarity in FDA's regulations by restoring inadvertently deleted regulatory text.

DATES: This rule is effective September 18, 2025.

FOR FURTHER INFORMATION CONTACT: Madhusoodana Nambiar, Office of Policy, Center for Devices and Radiological Health, 10903 New Hampshire Ave., Bldg. 66, Rm. 5519, Silver Spring, MD 20993–0002, 301–796–5837.

SUPPLEMENTARY INFORMATION:

I. Background

On January 20, 2023, FDA published a final rule entitled ''Radiological Health Regulations: Amendments to Records and Reports for Radiation Emitting Electronic Products; Amendments to Performance Standards for Diagnostic X-ray, Laser, and Ultrasonic Products'' (88 FR 3638, January 20, 2023). This rule amended § 1010.4(b) (21 CFR 1010.4(b)) to, among other things, permit manufacturers to submit applications for variances electronically and to remove the requirement for manufacturers to submit multiple paper copies of variance applications. FDA did not intend to make any other changes to § 1010.4(b). However, due to an error in FDA's amendatory instructions, FDA did not instruct the Office of the Federal Register to retain and renumber the prior content of § 1010.4(b)(1). As a result, the prior content of § 1010.4(b)(1)(i)–(xi), which listed the required elements of a variance application, was inadvertently deleted from the Code of Federal Regulations instead of retained and renumbered under § 1010.4(b)(2). This action corrects that error by restoring the inadvertently deleted regulatory text.

II. Description of the Technical Amendments

FDA is amending § 1010.4 by revising paragraph (b)(2) and adding paragraph