FDA Executive Summary

Prepared for the
September 7, 2023, meeting of the
Microbiology Devices Panel of the
Medical Devices Advisory Committee

Discussion and Recommendations for the Potential Future Reclassification of Certain Class III Infectious Disease In Vitro Diagnostic Devices Including Hepatitis B Virus Antigen, Antibody, and Molecular Assays, Parvovirus Antibody Assays, and Mycobacterium tuberculosis Interferon Gamma Release Assays

Discussion and Recommendations for In Vitro Diagnostic Devices

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i. Introduction, Purpose, and Structure of the Panel Meeting

The Division of Microbiology Devices (DMD) in the Office of Health Technology 7, *In Vitro* Diagnostics (OHT7), Office of Product Evaluation and Quality (OPEQ), Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA), has regulatory oversight of diagnostic assays for infectious diseases. FDA is convening this Microbiology Devices Panel (the Panel) of the Medical Devices Advisory Committee meeting on September 7, 2023, to discuss and make recommendations regarding the potential future regulatory reclassification of *in vitro* diagnostic devices (IVDs) for certain infectious diseases.

The session held on September 8, 2023, will be reserved for discussion of IVDs used in pandemic preparedness and response. The Executive Summary for this session will be provided separately.

The panel meeting will be held in a virtual format over the course of two days and includes time for FDA presentations, open public comment, questions by the panel, and panel deliberation.

a. Purpose and Structure of the Meeting

The purpose of this meeting is to discuss the potential future reclassification of the following devices:

1. Qualitative HBV antigen assays, qualitative HBV antibody assays, quantitative assays that detect anti-HBs [antibodies to HBV surface antigen (HBsAg)], quantitative HBV molecular assays, hereafter referred to as HBV assays (product codes LOM and MKT),

2. Qualitative Parvovirus B19V antibody assays (product codes MYM and MYL), and

3. Qualitative *Mycobacterium tuberculosis* (TB) cell mediated immune reactivity/Interferon Gamma Release assays (IGRA) (product codes NCD and OJN).

These tests are currently regulated as Class III devices, subject to premarket approval (PMA) and are under consideration for potential future reclassification into Class II (special controls) for which a premarket notification (510(k)) would be required. FDA is seeking recommendations from the Panel members and the public on whether sufficient information exists such that the development of special controls (which along with general controls) could mitigate the risks from some or all of these devices such that the devices would provide a reasonable assurance of safety and effectiveness and therefore, can be eligible for a Class II designation.

IVDs classified into Class III generally have greater FDA oversight and regulatory requirements than Class II devices. During the meeting, the Panel will be asked to deliberate on the risks associated with the above-mentioned devices, including discussion of whether class II is appropriate and potential special controls. The Panel will not be asked to formally vote on whether actual reclassification should occur, or to assess whether any specific device currently under development warrants reclassification. However, depending on the discussion at this meeting, there are two possible outcomes. Either it may become apparent that reclassification is not appropriate at this time or, alternatively, that special controls can be developed that would provide reasonable assurance of safety and effectiveness for these devices without the additional oversight accorded a device with Class III status and that FDA should pursue the reclassification process.

ii. Background

a. Regulation of IVDs

Per 21 CFR 809.3, *in vitro* diagnostic devices are defined as[1]:

> "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body…"

FDA regulations applicable to IVDs are based on the FDA classification of the device. The current approach to classification is a product of several laws, most prominently the 1976 Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (FD&C Act). [2] Medical devices, including IVDs, are classified based on the level of risk to patients. The three regulatory classes for device categorization are based on the level of control necessary to assure the safety and effectiveness of a device:

> Class I: Devices of low to moderate risk for which general controls are sufficient to provide a reasonable assurance of safety and effectiveness of the device.
>
> Class II: Devices of moderate to high risk for which require both general and special controls to provide a reasonable assurance of safety and effectiveness of the device.
>
> Class III: Devices of high risk for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness.

Figure 1 depicts a decisional chart detailing how FDA generally classifies medical devices based on the risks associated with the device and by evaluating regulatory controls that provide a reasonable assurance of the device's safety and effectiveness.

i. Class I Devices

Class I devices are primarily those devices for which general controls are determined to be sufficient to provide reasonable assurance of device safety and effectiveness. Devices may also be Class I where insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, but the device is not purported or represented to be for use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury.[3]

General controls are basic requirements not unique to any specific device but controls that are broadly applicable to medical device.[4] Examples of general controls include:

- Registration of manufacturing facilities and listing of products
- 510(k) premarket notification requirement
- Good manufacturing practices (GMPs)

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[1] All citations or references to the Code of Federal Regulations in this document are available at: https://www.ecfr.gov/current/title-21.
[2] https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls
[3] Section 513(a)(1)(A)(ii) of the FD&C Act; 21 CFR 860.3 Medical Device Classification Procedures
[4] See Section 513(a)(1)(A)(i) of the FD&C Act for a complete list of the general control statutory provisions.

- Notifications of risks and of repair, replacement, or refund
- Records and reports
- Restrictions on sale and distribution or use
- Other regulatory controls, e.g., labeling, adverse event reporting, misbranding, adulteration of the device

For example, Multipurpose culture medium devices are Class I as specified in the Code of Federal Regulations:

> 21 CFR 866.2300 Multipurpose culture medium.
>
> (a) *Identification*. A multipurpose culture medium is a device that consists primarily of liquid or solid biological materials intended for medical purposes for the cultivation and identification of several types of pathogenic microorganisms without the need of additional nutritional supplements. Test results aid in the diagnosis of disease and also provide epidemiological information on diseases caused by these microorganisms.
>
> (b) *Classification.* Class I (general controls).
> The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in § 866.9.

ii. Class II Devices

Class II devices are those that cannot be classified as Class I because general controls alone are insufficient to provide reasonable assurance of device safety and effectiveness, but where there is sufficient information to establish special controls that can provide such assurance.[5] Examples of special controls may include:

- performance standards
- postmarket surveillance
- patient registries
- special labeling requirement
- other appropriate action deemed necessary for mitigating the risks of the device

For example, a culture medium for pathogenic *Neisseria* spp. is a Class II device as specified in the Code of Federal Regulations:

> 866.2410 Culture medium for pathogenic *Neisseria* spp.
>
> (a) *Identification.* A culture medium for pathogenic *Neisseria* spp. is a device that consists primarily of liquid or solid biological materials used to cultivate and identify pathogenic *Neisseria* spp. The identification aids in the diagnosis of disease caused by bacteria belonging to the genus *Neisseria*, such as epidemic cerebrospinal meningitis, other meningococcal disease, and gonorrhea, and provides epidemiological information on these microorganisms.
>
> (b) *Classification.* Class II (performance standards)
>
> Class II submissions are reviewed by FDA under what is referred to as the 510(k) process, named after the section of the statute where the requirement is located. Under the 510(k) paradigm, a device can be cleared

[5] Section 513(a)(1)(B) of the FD&C Act.

for marketing if it is determined to be as safe and effective as a preexisting 'predicate' device (i.e., the device is 'substantially equivalent' to the predicate device).[6]

iii. Class III Devices

Class III devices are those for which insufficient information exists to determine that general and special controls can provide reasonable assurance of the safety and effectiveness, **and** where these devices are life supporting or life sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents unreasonable risk of illness or injury.[7] Class III devices require 'premarket approval' (PMA). FDA provides greater oversight over Class III devices than over Class II and Class I devices.[8]

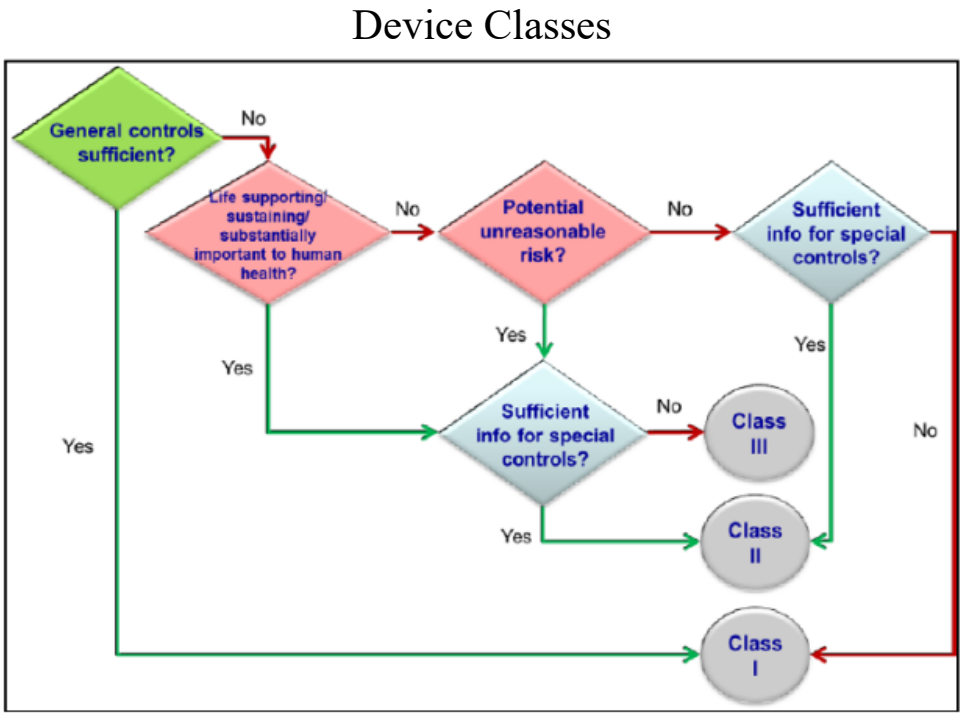

Figure 1: Under section 513(a) of the FD&C Act, FDA generally classifies medical devices based on the risks associated with the device and by evaluating regulatory controls that provide a reasonable assurance of the safety and effectiveness of the device.

[6] Devices which are submitted under a 510(k) are 'cleared' for marketing by FDA; under the PMA process (described below) devices are 'approved' by FDA.
[7] Section 513(a)(1)(C) of the FD&C Act.
[8] More detailed information regarding pre-market PMA applications is available at: https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma

b. Current Regulation of HBV Assays

i. Qualitative HBV Antigen Assays

FDA currently regulates qualitative HBV antigen assays as prescription IVDs intended for use in the detection of HBV antigens and may be used 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). Diagnosis of HBV infection should not be established based on a single test result, but should be determined in conjunction with clinical findings and other diagnostic procedures (e.g.: HBV serology and antigen testing, liver function, etc.)

Please refer to Table 1 below for a list of FDA approved HBV antigen assays. To date, FDA has approved 17 PMAs for the detection of HBV antigens. These tests are not intended for use in screening blood, plasma, or tissue donors. HBV antigen assays have an intended use such as the following (e.g.: HBs Antigen test):

> The [test name] is a [specify technology] for the qualitative detection of Hepatitis B surface antigen (HBsAg) in human adult and pediatric (2 years to 21 years of age) serum, serum separator tube, and plasma.
>
> The assay may also be used to screen for hepatitis B virus (HBV) infection in pregnant women to identify neonates who are at risk of acquiring hepatitis B during the perinatal period. Assay results, in conjunction with other laboratory results and clinical information, may be used to provide presumptive evidence of infection with HBV (state of infection or associated disease not determined) in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis B infection.

FDA currently regulates HBV antigen assays as Class III devices requiring a PMA application. During the upcoming panel meeting, the Panel will be asked to discuss recommendations regarding whether HBV antigen assays intended for the qualitative detection of HBV antigens can be potentially reclassified into Class II on the basis that there is sufficient information to establish special controls, which, in addition to general controls can provide reasonable assurance of the safety and effectiveness of the devices. Proposed special controls will be discussed in further detail at the upcoming panel meeting.

ii. Qualitative Antibody Assays

FDA currently regulates qualitative HBV antibody assays as prescription IVDs intended for use in the detection of antibodies to HBV and may be used 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 test result, but should be determined in conjunction with clinical findings and other diagnostic procedures (e.g.: HBV serology and antigen testing, liver function, etc.)

Please refer to Table 2 below for a list of FDA approved HBV qualitative antibody assays. To date, FDA has approved 38 PMAs for the detection of HBV antibodies. These tests are not intended for use in screening blood, plasma, or tissue donors. HBV antibody assays have an intended use such as the following (e.g.: Anti-HBc test):

> The [HBV antibody assay name] assay is an *in vitro* diagnostic immunoassay for use in the qualitative determination of total antibodies to the core antigen of the hepatitis B virus (HBV) in human adult serum

and plasma. This assay can be used as an aid in the diagnosis of adults with acute or chronic hepatitis B virus (HBV) infection, and in the determination of the clinical status of HBV-infected individuals in conjunction with other HBV serological markers, for the laboratory diagnosis of HBV disease associated with HBV infection. This assay can also be used as an aid in the differential diagnosis in individuals displaying signs and symptoms of hepatitis.

FDA currently regulates qualitative HBV antibody assays as Class III devices requiring a PMA application. During the upcoming panel meeting, the Panel will be asked to discuss recommendations regarding whether HBV antibody assays intended for the qualitative detection of antibodies to HBV can be potentially reclassified into Class II on the basis that there is sufficient information to establish special controls, which, in addition to general controls can provide reasonable assurance of the safety and effectiveness of the devices. Proposed special controls will be discussed in further detail at the upcoming panel meeting.

iii. Quantitative Antibody to Hepatitis B Surface Antigen (Anti-HBs) Assays

FDA currently regulates quantitative assays that detect anti-HBs as prescription IVDs that may be used as an 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.

Please refer to Table 3 below for a list of FDA approved quantitative anti-HBs assays. To date, FDA has approved 6 PMAs for the detection and quantitation of anti-HBs. Quantitative anti-HBs assays have an intended use such as the following:

> The [test name] assay is an *in vitro* quantitative determination of total antibodies to the hepatitis B surface antigen (HBsAg) in human adult, pregnant women, and pediatric (ages 2 to 21 years) serum and plasma (K_2EDTA and K_3EDTA). Assay results may be used as an aid in the determination of susceptibility to hepatitis B virus (HBV) infection for individuals prior to or following HBV vaccination; or where vaccination status is unknown.
> Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown. The detection of anti-HBs is indicative of laboratory diagnosis of seroconversion from hepatitis B virus (HBV) infection or from vaccination.

FDA currently regulates quantitative anti-HBs assays as Class III devices requiring a PMA. During the upcoming panel meeting, the Panel will be asked to discuss recommendations regarding whether quantitative anti-HBs tests can be potentially reclassified into Class II on the basis that there is sufficient information to establish special controls, which, in addition to general controls can provide reasonable assurance of the safety and effectiveness of the devices. Proposed special controls will be discussed in further detail at the upcoming panel meeting.

iv. HBV Molecular Assays

FDA currently regulates quantitative HBV molecular assays as prescription IVDs intended for the detection of HBV DNA in specimens from individuals with antibody evidence of HBV infection. In these devices, the detection of HBV DNA is used for management of patients undergoing anti-viral therapy for assessing response to treatment and NOT as a diagnostic for HBV infection.

Please refer to Table 4 below for a list of FDA approved quantitative HBV molecular assays. To date, FDA has approved five PMAs for the quantitative detection of HBV DNA. Quantitative HBV DNA assays have an intended use such as the following:

> The [test name] assay is an *in vitro* polymerase chain reaction (PCR) assay to quantitate Hepatitis B Virus (HBV) DNA in human plasma or serum. The assay is intended for use as an aid in the management of patients with chronic HBV infection undergoing anti-viral therapy. The assay can be used to measure HBV DNA levels at baseline and during treatment to aid in assessing response to treatment. The results from the assay must be interpreted within the context of all relevant clinical and laboratory findings.
>
> This assay is not intended to be used for screening donors of blood, blood products, or cell, tissue, and cellular and tissue-based products (HCT/Ps) or as a diagnostic test to confirm the presence of HBV infection.

FDA currently regulates quantitative HBV molecular assays as Class III devices requiring a PMA application. During the meeting, the panel will be asked to discuss recommendations regarding whether quantitative HBV DNA assays can be reclassified into Class II on the basis that there is sufficient information to establish special controls, which, in addition to general controls can provide reasonable assurance of the safety and effectiveness of the devices. Proposed special controls will be discussed in further detail at the upcoming panel meeting.

c. Current Regulation of Qualitative Parvovirus Antibody Assays

FDA currently regulates qualitative serology-based Parvovirus antibody assays as prescription IVDs intended for the detection of IgM antibody and IgG antibody evidence of B19 virus (human parvovirus B19) infection and may be used to aid in the diagnosis of past, recent, or current infection with B19 virus.

Please refer to Table 5 below for a list of FDA approved qualitative Parvovirus antibody assays. To date, FDA has approved four PMAs for the qualitative detection of Parvovirus antibodies. Qualitative serology-based Parvovirus antibody assays have an intended use such as the following:

> The [Parvovirus IgM antibody test name] assay is an enzyme-linked immunosorbent assay (ELISA) for the qualitative detection of IgM antibodies to B19 virus (B19V, previously known as human parvovirus B19) in human serum, lithium heparin, EDTA, and citrated plasma. This test in conjunction with the [Parvovirus IgG antibody test name], may be used for testing women of childbearing age to determine their serological status where there is a suspicion of exposure with B19V.
>
> The results of these assays may be used to make serological determination of past or current infection with B19V. The clinician should consider the results of these assays as presumptive for risk of fetal infection with B19V. The test may also be used for all patients as an aid in the diagnosis of fifth disease (erythema infectiosum).

FDA currently regulates qualitative serology-based Parvovirus antibody assays as Class III devices requiring a PMA. During the meeting, the panel will be asked to discuss recommendations regarding whether qualitative serology-based Parvovirus antibody assays can be reclassified into Class II on the basis that there is sufficient information to establish special controls, which in addition to general controls, can provide reasonable assurance of the safety and effectiveness of the devices. Proposed special controls will be discussed in further detail at the upcoming panel meeting.

d. Current Regulation of Qualitative *Mycobacterium tuberculosis* Interferon Gamma Release Assays

FDA currently regulates qualitative *Mycobacterium tuberculosis* (TB) cell mediated immune reactivity assays as prescription IVDs intended for the indirect detection of infection with *M. tuberculosis*. The immune response to infection with *M. tuberculosis* is predominantly a cell mediated immune response and results in sensitization of T-cell lymphocytes specific to *M. tuberculosis* antigens. *M. tuberculosis* interferon gamma release assays (IGRAs) are cell mediated immune reactivity tests that are intended to aid in the diagnosis of TB by detecting the release of interferon gamma from cells following stimulation with *M. tuberculosis* antigens.

Please refer to Table 6 below for a list of FDA approved qualitative *M. tuberculosis* cell mediated immune reactivity tests. To date, FDA has approved three PMAs for the qualitative detection of *M. tuberculosis* cell mediated immune reactivity. Qualitative *M. tuberculosis* cell mediated immune reactivity tests have an intended use such as the following:

> The [*M. tuberculosis* cell mediated immune reactivity test name] assay is an *in vitro* diagnostic test for the detection of effector T cells that respond to stimulation by *Mycobacterium tuberculosis* antigens ESAT-6 and CFP-10 by capturing interferon gamma (IFN-y) in the vicinity of T cells in human whole blood collected in sodium citrate or sodium or lithium heparin. It is intended for use as an aid in the diagnosis of *M. tuberculosis* infection.
>
> The [*M. tuberculosis* cell mediated immune reactivity test name] assay is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

FDA currently regulates qualitative *M. tuberculosis* cell mediated immune reactivity assays as Class III devices requiring a PMA. During the meeting, the panel will be asked to discuss recommendations regarding whether qualitative *M. tuberculosis* cell mediated immune reactivity assays can be reclassified into Class II on the basis that there is sufficient information to establish special controls, which, in addition to general controls can provide reasonable assurance of the safety and effectiveness of the devices. Proposed special controls will be discussed in further detail at the upcoming panel meeting.

iii. Clinical Setting

a. Clinical Setting of HBV Infection

i. Public Health Burden

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.[9] It is estimated by the Centers for Disease Control and Prevention (CDC) that chronic HBV infection in the United States (US) affects at least between 580,000 to 1.17 million people with HBV infection in the US; two-thirds of whom may be unaware of their infection[10]. HBV infection can be asymptomatic, and accordingly, many HBV-infected individuals are unaware of their HBV infection. Approximately 95% of adult patients with acute infection, defined as the first six months after infection, recover completely, and 5% of adults develop chronic HBV[11] 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% risk of progression to chronic HBV and up to 25% of infants who acquire chronic HBV infection will die prematurely from HBV-related hepatocellular carcinoma or cirrhosis[12.] 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.[13] HBV is a vaccine-preventable liver infection.

With the initiation of the WHO Viral Hepatitis Elimination Plan[14]and the Department of Health & Human Services (HHS) Viral Hepatitis National Strategic Plan for the United States,[15] 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.[16]

Once an individual is tested and diagnosed as HBV infected, HBV DNA testing is performed to inform treatment decisions. While HBV infection is treatable, it is not curable which means that most people who start HBV anti-viral 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[17]. Thus, identifying individuals who are HBV infected, linking them to care, and managing their HBV infection to alleviate development of liver damage, liver cancer,

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[9] Hepatitis B (who.int) Accessed on July 25, 2023.
[10] Centers for Disease Control and Prevention - Viral Hepatitis Q&As for Health Professionals (Available at https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview). Accessed on July 25, 2023.
[11] Centers for Disease Control and Prevention - Viral Hepatitis Q&As for Health Professionals (Available at https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview) Accessed on July 25, 2023.
[12] Centers for Disease Control and Prevention - Viral Hepatitis Q&As for Health Professionals (Available at https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview). Accessed on July 25, 2023.
[13] Terrault, NA et, al., "Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance." Hepatology, 67(4): 1560-1599, 2018.
[14] https://www.who.int/health-topics/hepatitis/elimination-of-hepatitis-by-2030#tab=tab_1 Accessed on July 25, 2023.
[15] https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf Accessed on July 25, 2023.
[16] https://www.cdc.gov/hepatitis/hbv/index.htm Accessed on July 25, 2023.
[17] Terrault, NA et, al., "Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance." Hepatology, 67(4): 1560-1599, 2018.

liver failure and potential HBV virus transmission would not only greatly impact public health but also go a long way towards helping the US achieve HBV elimination.

ii. Testing for HBV

CDC recommends use of the triple panel test which includes: HBsAg, anti-HBs, and anti-HBc to identify the stage of HBV infection[18]. Other markers include HBV DNA, HBeAg and anti-HBe, where detection and quantitation of HBV DNA is a measure of viral load, detection of HBeAg is a marker for viral replication, and detection of anti-HBe could be used to monitor response to treatment in chronic HBV patients. The following table shows CDC's interpretation of the HBV serological testing results[19]:

Test and Result	Interpretation	Action
HBsAg—Positive Total anti-HBc — Positive IgM anti-HBc — Positive Anti-HBs — Negative	Acute infection	Link to hepatitis B care
HBsAg — Positive Total anti-HBc — Positive IgM anti-HBc — Negative[1] Anti-HBs — Negative	Chronic Infection	Link to hepatitis B care
HBsAg — Negative Total anti-HBc — Positive Anti-HBs — Positive	Resolved Infection	Counsel about HBV infection reactivation risk
HBsAg — Negative Total anti-HBc — Negative Anti-HBs — Positive[2]	Immune from receipt of prior vaccination (if documented complete series)	If no documentation of full vaccination, then complete vaccine series per ACIP recommendations.
HBsAg — Negative Total anti-HBc — Positive Anti-HBs — Negative	*Only core antibody is positive. See possible interpretations and corresponding actions:*	
	Resolved infection where anti-HBs levels have waned	Counsel about HBV infection reactivation risk
	Occult Infection	Link to hepatitis B care
	Passive transfer of anti-HBc to an infant born to an HBsAg-positive gestational parent	No action
	A false positive, thus patient is susceptible	Offer HepB vaccine per Advisory Committee on Immunization Practices (ACIP)
	A mutant HBsAg strain that is not detectable by laboratory assay	Link to hepatitis B care
HBsAg — Negative Total anti-HBc — Negative Anti-HBs — Negative[3]	Susceptible, never infected (if no documentation of HepB vaccine series completion)	Offer HepB vaccine per ACIP recommendations

[1] IgM anti-HBc also might be positive in persons with chronic infection during severe HBV infection flares or reactivation.

[2] Immune if anti-HBs concentration is >10 mIU/mL after vaccine series completion.

[18] Erin E. Conners, Lakshmi Panagiotakopoulos, Megan G. Hofmeister, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations — United States, 2023. MMWR Recomm Rep 2023;72(No. RR-1):1–25. DOI: http://dx.doi.org/10.15585/mmwr.rr7201a1

[19] Interpretation of Hepatitis B Serologic Test Results | CDC: https://www.cdc.gov/hepatitis/hbv Accessed July 25, 2023.

[3] Anti-HBs concentrations might wane over time among vaccine responders. People with a documented, complete HepB vaccine series typically do not need to be revaccinated, except for special populations like patients on hemodialysis or health care personnel.

b. Clinical Setting of Parvovirus Infection

i. Public Health Burden

Human Parvovirus B19 (B19V) infection represents a significant global public health burden. B19V infection is common worldwide, and according to the CDC approximately 50% of all adults have been infected with B19V, most likely contracted in childhood or adolescence. The percentage of people with measurable B19V increases with increasing age. Those who have previously been infected with the virus are typically considered immune and are protected against future B19V infection. Immunoglobulin antibodies to B19V in the serum, present in half of the adult population, likely indicates immunity is acquired to the virus during childhood.[20] When considering people who are or may become pregnant, approximately 50% of individuals of child-bearing age and 30-40% of individuals who are pregnant, are susceptible to B19V infection, which puts the fetus at risk.[21] In the United States, B19V often infects people in late winter, spring, and early summer, and mini-outbreaks of B19V infection occur every 3 to 4 years.

There are three modes of transmitting B19V infection: respiratory, vertical, and hematogenous. The most common mode of transmission is via the respiratory route, such as saliva, sputum, or nasal mucus when a person who is infected coughs or sneezes and is typically acquired by young children. The virus can be transmitted through person-to-person contact, fomites, and respiratory secretions and/or saliva. The risk of transmission is increased in situations where there is close contact amongst individuals (e.g., daycares, schools, etc.) The virus bears a direct cytotoxic effect on erythroid cells and can lead to anemia/a decrease in hemoglobin during infection. Chronic or reactivated infection can be associated with increased morbidity for high-risk populations such as immunocompromised patients or those with hemolytic anemia. Vertical transmission occurs when a susceptible pregnant individual is infected with B19V. The virus can be transmitted to the fetus causing serious complications such as miscarriage, intrauterine fetal death, and hydrops fetalis. Hematogenous transmission has been known to occur through blood and blood products.

B19V infection is often the most typical cause of fifth disease, or erythema infectiosum (EI), which is a mild rash illness that commonly affects children; however, adults infected with B19V can also develop into fifth disease, as well. Other symptoms of B19V infection include painful or swollen joints and severe anemia. In infrequent cases, several of the symptoms can persist.[22] Symptoms associated with B19V infection only present once the contagious stage of the infection has concluded.

According to the CDC, there is currently no vaccine or medicine that can prevent B19V infection. Routine fever reducing medication can be effective in treating fevers in B19V patients. Nonsteroidal anti-inflammatory medication can alleviate joint pain and swelling. Individuals who are of good health, typically do not require treatment. Infection persists until the infected person develops immunoglobulins against the virus, meaning the virus will subside on its own once a person's immune system is able to properly defend itself.

[20] https://emedicine.medscape.com/article/961063-overview
[21] Virology, epidemiology, and pathogenesis of parvovirus B19 infection - UpToDate
[22] https://www.cdc.gov/parvovirusb19/about-parvovirus.html

ii. Testing for Parvovirus

The diagnostic approach to Parvovirus starts with a high index of suspicion based on presentation of symptoms consistent with Parvovirus infection. For most cases, B19V testing is typically not necessary as symptoms are often mild and do not persist or cause harm. Testing may occur if an individual at risk for complications may have been recently infected. Individuals at risk for complications include those with iron deficiency anemia or conditions that impact red blood cells (e.g., sickle cell anemia), pregnant individuals, or those with compromised immune systems.

Enzyme-linked immunosorbent assays (ELISA) test for active, recent, or past B19V infection by detecting IgM and/or IgG class antibodies to B19V in human blood (serological testing). ELISA-based methods for detection of antibodies to Parvovirus have been approved by FDA. Serological assays typically employ recombinant VP1 and/or VP2 viral antigens, and their sensitivity and specificity depend on the choice of antigens. IgM-antibody assays are the most sensitive test to detect recent B19V infection while IgG assays detect previous infection, which infers immunity. It has been shown that performance of anti-B19V IgM tests benefits from depletion of IgG antibodies from the sample.[23]

There are other technologies that have been employed as an aid in the diagnosis of Parvovirus infection. These methods detect the presence of the virus or anti-B19V antibodies and include light and electron microscopy, nucleic acid amplification-based techniques (NAAT), antigen detection with immunohistochemical techniques, viral isolation, immunofluorescence, and Western blot analysis, however none of these methods are approved by FDA.[24]

Viral DNA can be detected using NAAT-based assays such as real-time PCR, several of which are commercially available outside the US. Since a WHO International Standard for parvovirus B19 DNA is available, standardized quantitative NAAT assays can be potentially developed to determine viral load, although their diagnostic value is unclear[23].

c. Clinical Setting of *Mycobacterium tuberculosis* Infection

i. Public Health Burden

Tuberculosis is a bacterial infection caused by species of the *M. tuberculosis* complex (MTBC).[25] Pulmonary tuberculosis is the most common clinical presentation of tuberculosis in adults, although extra-pulmonary disease is relatively more prevalent in children. Infection with *Mycobacterium tuberculosis* (TB) is the most common cause of pulmonary tuberculosis. Although infection with any member of the MTBC can lead to pulmonary tuberculosis, *M. bovis* is the cause of active pulmonary tuberculosis in less than 2% of subjects in the United States,[26] and infection due to members of MTBC other than *M. bovis* and *M. tuberculosis* is rare in the United States. Infection occurs by transmission of the organism to a new host through inhalation of airborne particles that contain MTBC released from individuals with active pulmonary disease.

Most people who are infected with TB are asymptomatic, which is known as latent tuberculosis infection; latent infections are not contagious and do not result in clinical disease in most cases. In some people, this organism

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[23] Clinical manifestations and diagnosis of parvovirus B19 infection - UpToDate
[24] Current Trends Risks Associated with Human Parvovirus B19 Infection (cdc.gov)
[25] *M. tuberculosis* complex includes the following species: *M. tuberculosis, M. bovis, M. africanum, M. canettii*, *M. microti, M. caprae, M. pinnipedii, M. mungi and M. orygis, M. suricatte*.
[26] Centers for Disease Control and Prevention Bovine TB in Humans Fact Sheet - *Mycobacterium bovis* (Bovine Tuberculosis) in Humans. Division of Tuberculosis Elimination. Accessed on July 6, 2023. http://www.cdc.gov/tb/publications/factsheets/general/mbovis.htm.

overcomes the defenses of the immune system, resulting in progression from latent tuberculosis infection to active TB disease either relatively soon after infection or after long periods of latency, usually lasting decades. Overall, there is a 5-10% lifetime risk for patients with latent infection to develop active TB disease; however, the risk varies due to many factors, and may be substantially increased by immunosuppression.[27]

TB infection represents a significant global public health burden, specifically infections caused by multidrug-resistant TB. According to the WHO, approximately 25% of the global population has been infected with TB. In 2021, an estimated 10.6 million people globally were sicked by TB and 1.6 million people died from TB infection, including 187,000 HIV positive persons.[28] The incidence of active TB has been steadily declining in the United States since 1953, except for a brief period of increase of active TB in HIV co-infected patients between 1989-1992. [29] Following a substantial decrease in reported cases in 2020, reported cases of TB and TB incidence began increasing in 2021 and are returning to pre-pandemic levels following presumed underreporting during the COVID-19 pandemic.[30] There were 8,300 provisional cases of active TB reported to the CDC in 2022, and approximately 73% of TB cases in the United States occurred among non-U.S. born persons. Of the approximately 85% of cases with known HIV status, 4.7% of cases were in individuals co-infected with HIV and TB. While the true prevalence of latent TB infection (LTBI) is unknown, CDC estimates that the infection may be present in up to 13 million people in the United States. Of the United States TB cases, more than 80% are attributed to reactivation of untreated LTBI.[31,32]

The bacille Calmette-Guérin (BCG) vaccine is used in many countries with a high prevalence of TB to prevent against TB meningitis and disseminated TB disease in children. BCG is not generally recommended for use in the United States due to the low risk of infection in the U.S., the variable effectiveness against adult pulmonary TB and the potential for vaccine interference with tuberculin skin test reactivity.[33] Numerous antibiotic regimens to treat LTBI and active TB disease are available. Adverse drug reactions are common, and patients should be closely monitored while on therapy. Tuberculosis that is resistant to at least isoniazid and rifampin, is called multidrug-resistant TB (MDR TB). Extensively drug resistant tuberculosis (XDR TB) is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs.[34]

ii. Indirect Tests for *Mycobacterium tuberculosis*

There are currently two types of indirect tests for the detection of TB infection: the Mantoux tuberculin skin test (TST) and the interferon gamma release assay (IGRA). The TST, consists of the intradermal injection of tuberculin purified protein derivative (PPD) into the inner surface of the forearm. The skin test reaction should be read by a

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[27] Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR 2011;60:1650–1653 and 33 Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6).
[28] Tuberculosis (who.int)
[29] CDC MMWR, Vol. 62, No. 11; 201-205. Reported Tuberculosis in the United States, 2012.Atlanta, GA: U.S. Department of Health and Human Services, CDC, March, 2013.
[30] CDC MMWR, Vol. 72, No. 12; 297--303. *Tuberculosis -- United States*, *2022*.Atlanta, GA: U.S. Department of Health and Human Services, CDC, March, 2023.
[31] Centers for Disease Control and Prevention. Tuberculosis (TB). Latent TB Infection in the United States- Published Estimates. July 6, 2023. http://www.cdc.gov/tb/statistics/ltbi.htm
[32] Shea KM, Kammerer JS, Winston CA, Navin TR, Horsburgh CR Jr. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. *Am J Epidemiol*. 2014;179(2):216–225.
[33] Centers for Disease Control and Prevention. Tuberculosis (TB). BCG Vaccine Fact Sheet. Accessed on July 12, 2023. http://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm
[34] Centers for Disease Control and Prevention. Tuberculosis (TB). Multidrug-Resistant Tuberculosis (MDR TB) Fact Sheet. Accessed on July 12, 2023. http://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm

trained healthcare provider between 48 and 72 hours after administration. The reaction is measured in millimeters of induration with interpretation of the test dependent on the measurement and the person's risk of TB infection or risk of progression to TB disease if infected.[35] Previous BCG vaccination and infection with nontuberculous mycobacteria can cause reaction to the TST.

IGRAs are *in vitro* blood tests of cell-mediated immune response which measure T-cell release of IFN-γ following stimulation by peptide antigens such as ESAT-6 and CFP-10, which are specific to organisms in the M. TB complex.[36] These peptide antigens are absent from all BCG strains and most nontuberculous mycobacteria apart from *M. marinum, M. kansasii,* and *M. szulgai*. Because IGRAs are blood tests not affected by BCG vaccination status and do not require follow up evaluation, they are useful for evaluation of BCG vaccinated persons and in clinical scenarios where a single patient visit is advantageous. [37]

v. Risks to Health

The risks to health related to these devices identified by FDA include those related to the risk of false results (false positive, false negative, inaccurate low test result, inaccurate high test result, false reactive, or 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.

After consideration of the recommendations of professional organizations, other government organizations, FDA's accumulated experience from Medical Device Reporting (MDR), PMA applications, and the published peer-reviewed literature, FDA has identified the following additional specific risks associated with each of the IVD devices identified below.

a. Qualitative HBV Antigen Assays

The risks associated with qualitative HBV antigen assays, when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results, and failure to correctly operate the device. Factors that may cause decreased test 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.

vi. *A false positive test result for HBeAg*, incorrectly interpreting the test results as a positive test result, or failing to correctly operate the test causing a false positive test 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

[35] Centers for Disease Control and Prevention. Tuberculosis (TB). Tuberculin Skin Testing Fact Sheet. Accessed on July 12, 2023. https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm
[36] Pai M, Denkinger CM, Kik SV, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. *Clin Microbiol Rev*. 2014;27(1):3-20.
[37] Centers for Disease Control and Prevention. Tuberculosis (TB). IGRAs- Blood Tests for TB Infection Fact Sheet. Accessed on July 12, 2023. http://www.cdc.gov/tb/publications/factsheets/testing/igra.htm

patients who are coinfected but undiagnosed with other viruses that are treated with the same antiviral medication, such as HIV, can lead to viral resistance.

vii. *A false positive test result for HBsAg,* incorrectly interpreting the test results as a positive test result, or failing to correctly operate the test causing a false positive test 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 positive test reporting include cross-reactivity with antigens from other microorganisms or other disease conditions.

viii. *A false negative result for HBeAg,* incorrectly interpreting the test results as a negative test result, or failing to correctly operate the test causing a false negative test 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.

ix. *A false negative test result for HBsAg,* incorrectly interpreting the test results as a negative test result, or failing to correctly operate the test causing a false negative test 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 negative HBsAg test 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)

The risks associated with HBV antibody assays, when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results and failure to correctly operate the devices. Factors that may cause decreased test 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 positive results include device contamination from positive samples, cross-reactivity with other antibodies, or misinterpretation of invalid results as reactive.

i. *A false positive test result for anti-HBs and anti-HBc,* incorrectly interpreting the test results as a positive test result, or failing to correctly operate the test causing a false positive test result may lead to improper patient management. A false positive antibody test 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 coinfected but undiagnosed with other viruses that are treated with the same antiviral medication, such as HIV, can lead to viral resistance. Consequently, repeatedly false positive results have the potential to lead to inappropriate patient management decisions.

ii. *A false positive test result for Anti-HBs,* incorrectly interpreting the test results as a positive test result, or failing to correctly operate the test causing a false positive test 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.

iii. *A false positive test result for anti-HBe,* incorrectly interpreting the test results as a positive test result, or failing to correctly operate the test causing a false positive test 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 (update reference) or may contribute to public health risk by leading to inadvertent transmission of virus by an infected individual.

iv. *A false negative test 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 test results as a negative test result, or failing to correctly operate the test causing a false negative test 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 negative results can also lead to unnecessary diagnostic evaluation if alternative etiologies of hepatitis are pursued. False negative test results may occur if the level of antibody in a specimen is below the limit of detection of the assay.

v. *A false negative test 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 test results as a negative test result or failing to correctly operate the test causing a false negative test result may lead to unnecessary repeated vaccination for HBV.

vi. *A false negative test result for anti-HBe,* incorrectly interpreting the test results as a negative test result or failing to correctly operate the test causing a false negative test 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 Molecular Assays

The risks associated with the quantitative HBV molecular assays when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results, and failure to correctly operate the device.

Decreased test sensitivity and/or an increased rate of false negative test 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:

i. *A false positive or falsely elevated quantitative HBV molecular assay result,* incorrectly interpreting the test results as a positive test result or failing to correctly operate the test causing a false negative test 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 molecular assay results may not undergo liver biopsy to investigate other causes of liver disease when the biopsy would otherwise be indicated for certain patients.

ii. *A false negative or falsely decreased quantitative HBV molecular assay result*, incorrectly interpreting the test results as a negative test result, or failing to correctly operate the test causing a false negative test 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 molecular assay results may undergo liver biopsy to investigate other causes of liver disease.

d. Qualitative Parvovirus Antibody Assays

The risks associated with the qualitative Parvovirus antibody assays, when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results, and failure to correctly operate the device. Decreased test sensitivity and specificity and/or an increased rate of false reactive or non-reactive test reporting may occur with patient samples that contain other antibodies or interfering substances. Parvovirus antibody concentrations can be below the detection limit of the assay early in disease progression:

i. *False reactive results*, *false non-reactive results*, *failure to correctly interpret test results, or failure to correctly operate the device causing a false reactive or non-reactive result* incur the primary risks associated with these assays.

ii. *False non-reactive Parvovirus antibody assay results,* incorrectly interpreting the test results as non-reactive test results, or failing to correctly operate the test causing non-reactive test results could lead to spreading of the virus to others and improper patient management, such as awareness of potential for chronic or recurrent Parvovirus infection in immunocompromised individuals and its associated increase in morbidity, or awareness of potential sequelae to the fetus in a pregnant patient. Treatment is largely supportive and only provided to patients with other clinical signs and symptoms of severe disease.

iii. *False reactive Parvovirus antibody assay results,* incorrectly interpreting the test results as false reactive test results, or failing to correctly operate the test causing false reactive test results may result in less frequent monitoring of pregnant individuals; however, most pregnant individuals undergo routine ultrasound monitoring during their pregnancy. False reactive results could also lead to

unnecessary isolation of individuals and unnecessary psychosocial stressors related to positive Parvovirus antibody results. Parvovirus B19 IgG assay results should be interpreted with the results of a Parvovirus B19 IgM assay, which further mitigates the risks of false positive results.

e. *M. tuberculosis* Cell Mediated Immune Reactivity/Interferon Gamma Release Assays

The probable risks associated with *M. tuberculosis* cell mediated immune reactivity/interferon gamma release assays (TB IGRAs), when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results, and failure to correctly operate the device. Factors that may cause an increased rate of false results, include but are not limited to, incorrect blood sample collection or improper handling of the specimen affecting lymphocyte function, inaccurate lymphocyte quantification, and co-morbid conditions that affect immune functions.

Based on FDA's accumulated experience from PMA applications, from Medical Device Reporting (MDR), and the published literature, FDA has identified the following specific risks associated with TB IGRA devices.

i. *A false negative TB IGRA test result,* incorrectly interpreting the test results as a negative test result, or failing to correctly operate the test causing a false negative test result may lead to a non-diagnosis or delay in diagnosis of active or latent TB infection, with an associated delay in therapy and potential for progression of active infection or reactivation of latent TB disease which can contribute to an increased risk of TB-related morbidity or mortality. Additionally, a false negative result may facilitate the spread of *M. tuberculosis* to other individuals in their community.

   A false negative TB IGRA test result, incorrectly interpreting the test results as a negative test result, or failing to correctly operate the test causing a false negative test result may represent a missed opportunity for evaluation and subsequent treatment of underlying immunocompromising conditions such as human immunodeficiency virus (HIV) as well as a missed opportunity to provide antimicrobial therapy for latent tuberculosis infection.

ii. *A false positive TB IGRA test result*, incorrectly interpreting the test results as a positive test result, or failing to correctly operate the test causing a false positive test result may contribute to improper patient management including unnecessary additional testing and radiologic imaging, patient isolation, public health contact tracing leading to wasted healthcare resources as well as unnecessary antimicrobial treatment for TB infection with associated drug toxicities.

v. Special Controls

We anticipate robust discussion of potential special controls at the panel meeting. Possible considerations based on recent De Novos granted by OHT7 could include but are not limited to the following:

a. Requiring certain information in the labeling such as the following: analytes the device detects, the specimen types tested, the results provided to the end user, the clinical indications for which the test is to be used, the specific intended population(s), the intended use locations including testing location(s) where the device is to be used (if applicable), and other conditions of use, as appropriate.

b. Additional device specific labeling requirements such as statements on device labeling indicating that results should only be interpreted by health care providers with expertise in the [management of patients post-transplantation], and that the test is intended to be used in conjunction with the patient's medical history, clinical signs and symptoms, and results from other relevant laboratory findings.

c. Required analytical studies (e.g., inclusivity, cross-reactivity, interfering substances, competitive inhibition, carryover/cross contamination, matrix equivalency, hook effect, specimen stability, precision, and reproducibility)

d. Required clinical studies

vi. Questions

The reclassification of a device from Class III to Class II is dependent on the extent to which special controls, along with the applicable general controls, are sufficient to provide reasonable assurance of safe and effective use of the diagnostic device. In this context, the Panel is asked to please discuss the following:

1. HBV Assay Questions

1. Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by the following devices:

   (1) Qualitative HBV Antigen assays, (see section iv. a of this document)
   (2) Qualitative HBV Antibody assays, (see section iv. b of this document)
   (3) Quantitative Anti-HBs assays, and/or (see section iv. b of this document)
   (4) Quantitative HBV Molecular assays. (see section iv. c of this document)

   Please comment on whether you disagree with any of these identified risks or whether you believe any other risk should be included in the overall risk assessment of the devices listed above.

2. Please discuss potential mitigation measure(s)/control(s) that FDA should consider that could mitigate each of the identified risks (see section v of this document).

3. Based upon the information presented and future discussion at this panel meeting, please discuss whether, based on the available information, the Panel believes FDA should initiate the reclassification process for these devices from Class III to Class II, subject to special controls.

4. Currently, there are no FDA authorized tests for the detection and quantitation of HBsAg. Please discuss the appropriate intended use for such a device, potential risks associated with that intended use, and whether mitigation measures(s)/special control(s) could be developed that, in addition to general controls, to mitigate the risks to health.

2. Parvovirus Antibody Assay Questions

1. Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by Parvovirus antibody assays (see section iv. d of this document).

   Please comment on whether you disagree with any of these identified risks or whether you believe any other risk should be included in the overall risk assessment of Parvovirus antibody assays (see section iv. d of this document).

2. Please discuss potential mitigation measure(s)/control(s) that FDA should consider that could mitigate each of the identified risks (see section v of this document).

3. Based upon the information presented and future discussion at this panel meeting, please discuss whether, based on the available information, the Panel believes FDA should initiate the reclassification process for these devices from Class III to Class II, subject to special controls.

3. *M. tuberculosis* Assay Questions

1. Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by *M. tuberculosis* assays (see section iv. e of this document).

   Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of *M. tuberculosis* assays (see section iv. e of this document).

2. Please discuss potential mitigation measure(s)/control(s) that FDA may should consider that could mitigate each of the identified risks (see section v of this document).

3. Based upon the information presented and future discussion at this panel meeting, please discuss whether, based on the available information, the Panel believes FDA should initiate the reclassification process for this device from Class III to Class II, subject to special controls.

vii. Appendix

1. Table 1: HBV Antigen Devices

Manufacturer	Device	PMA Number	Date of Approval	PPA [95% CI]*#	NPA [95% CI]*#
DIASORIN INC.	DIASORIN ETI-EBK PLUS ASSAY	P990043	2/8/2001	96.75% [80.2% - 94.1%]	99.6% [98.7% - 100%]
DIASORIN INC.	DIASORIN ETI MAK-2 PLUS ASSAY	P990038	3/30/2001	100% [95.77% - 100%]	99.26% [95.92% - 99.87%]
Ortho-Clinical Diagnostics Inc.	VITROS IMMUNODIAGNOSTIC PRODUCTS/HBSAG REAGENT PACKVITROS IMMUNODIAGNOSTIC PRODUCTS CONFIRMATORY KIT AND VITROS IMMUNR	P000044	4/27/2001	90% [81.49% - 94.85%]	99.4% [99.05% - 99.7%]
ROCHE DIAGNOSTICS CORP.	ELECSYS HBSAG IMMUNOASSAY ELECSYS HBSAG CONFIRMATORY AND PRECICONTROL HBSAG	P990012	6/1/2001	100% [98.87% - 100%]	98.9% [93.49% - 99.79%]
Siemens Healthcare Diagnostics Products LTD	IMMULITE 2000 XPI HBSAG	P010050	7/26/2002	97.37% [90.9% - 99.28%]	99.02% [96.51% - 99.73%]
SIEMENS HEALTHCARE DIAGNOSTICS	ADVIA CENTAUR HBSAG READY PACK REAGENTS/CONFIRMATORY READY PACK REAGENTS/QUALITY CONTROL MATERIAL	P030049	5/26/2005	94.57% [89.14% - 97.79%]	99.63% [99.24% - 99.85%
ABBOTT LABORATORIES INC	AXSYM HBSAG HBSAG CONFIRMATORY AND AXSYM HBSAG CONTROLS	P050049	6/1/2006	95% [89.35% - 99.95%]	99.49% [99.07% - 99.76%]
Abbott Laboratories	ARCHITECT HBSAG REAGENT KIT CALIBRATORS CONTROLS CONFIRMATORY REAGENT KIT CONFIRMATORY MANUAL DILUENT	P060007	9/7/2006	98.77% [95.61% - 99.66%]	99.34% [98.87% - 99.61]
Ortho-Clinical Diagnostics Inc.	VITROS IMMUNODIAGNOSTIC PRODUCTS HBEAG REAGENT PACK/PRODUCTS HBEAG CALIBRATOR/PRODUCTS HBE CONTROLS	P090028	5/11/2011	99.3% [78.63% - 98.15%]	99.69% [99.32% - 99.86%]

SIEMENS HEALTHCARE DIAGNOSTICS	ADVIA CENTAUR HBEAG ASSAY AND QUALITY CONTROL MATERIAL	P090024	10/11/2011	90% [79.5% - 96.2%]	96.4% [95.3% - 97.2%]
Abbott Laboratories	ARCHITECT HBSAG QUALITATIVE QUALITATIVE CONFIRMATORY CONFIRMATORY MANUAL DILUENT CALIBRATORS AND CONTROLS	P110029	4/12/2012	97.83% [92.37% - 99.74%]	99.3% [98.81% - 99.63%]
ROCHE DIAGNOSTICS OPERATIONS INC	ELECSYS® HBEAG IMMUNOASSAY AND ELECSYS® PRECICONTROL HBEAG	P130015	3/14/2014	97.73% [88.18% - 99.6%]	99.58% [99.65% - 99.99%]
SIEMENS CORP.	ADVIA CENTAUR HBSAGII	P110041	5/16/2014	96.5% [92% - 98.8%]	99.8% [99.5% - 100%]
ROCHE DIAGNOSTICS INC.	Elecsys HBsAg II/Elecsys HBsAg Confirmatory Test/ PreciControl HBsAg II	P160019	12/23/2016	100% [91% - 100%]	99.8% [99.4% - 99.9%]
DiaSorin Inc.	LIAISON® XL MUREX HBeAg LIAISON® XL MUREX Control HBeAg	P180048	8/29/2020	97.48% [93.71% - 99.02%]	99.79% [99.55% - 99.91%]
DiaSorin Inc	LIAISON® XL MUREX HBsAg Qual LIAISON® MUREX Control HBsAg and LIAISON® XL MUREX HBsAg Confirmatory Test	P190017	8/29/2020	98.3% [96% - 99.3%]	99.80% [99.5% - 99.9%]
Abbott Laboratories	ARCHITECT HBsAg Next Qualitative Reagent Kit ARCHITECT HBsAg Next Confirmatory Reagent Kit ARCHITECT HBsAg NEXT Qualitative Calibrators	P210003	8/10/2022	100% [96.87% - 100%]	99.78% [99.44% - 99.91%]

*Overall PPA and NPA with their corresponding 95% CI. Note the overall PPA and NPA might not include the performance of the device in certain populations such as pregnant subjects and pediatrics.

When clinical study included samples collected and tested in the US and OUS, performance provided in this table is for samples collected and tested in the U.S.

2. Table 2: Qualitative HBV Antibody Devices

Manufacturer	**Device**	**PMA Number**	**Date of Approval**	**PPA [95% CI]*#**	**NPA [95% CI]*#**
Ortho-Clinical Diagnostics Inc.	VITROS IMMUNODIAGNOSTIC PRODUCTS:ANTI-HBS REAGENT PACK/ANTI-HBS CALIBRATORS	P000014	9/29/2000	93.2% [90.7%-95.2%]	94.1% [93% - 95.6%]
DIASORIN INC.	DIASORIN ETI-AB-AUK PLUS ASSAY	P990042	3/30/2001	Refer to SSED summary	

DIASORIN INC.	DIASORIN ETI-AB-COREK PLUS ASSAY	P990045	3/30/2001	Refer to SSED summary	
DIASORIN INC.	DIASORIN ETI-AB-EBK PLUS ASSAY	P990041	3/30/2001	Refer to SSED summary	
DIASORIN INC.	DIASORIN ETI-CORE-IGMK PLUS ASSAY	P990044	3/30/2001	Refer to SSED summary	
ROCHE DIAGNOSTICS CORP.	ELECSYS ANTI-HBS	P010054	2/28/2002	96.7% [90.8% – 99.3%]	99.8% [98.9% – 100.0%]
Siemens Healthcare Diagnostics Products LTD	IMMULITE 2000 XPI ANTI-HBC	P010051	7/24/2002	91.8% [81.9% - 97.3%]	99.3% [96.3% - 100.0%]
Siemens Healthcare Diagnostics Products LTD	IMMULITE 2000 XPI ANTI-HBC IMG	P010053	7/26/2002	85.7% [42.1% - 99.6%]	97% [94.25 - 98.7%]
Ortho-Clinical Diagnostics Inc.	VITROS IMMUNODIAGNOSTIC PRODUCTS ANTI-HBC IGM REAGENT PAK/CALIBRATOR	P030026	3/4/2004	63.16% [38.36% - 83.71%]	99.76% [99.39% - 99.93%]
ORTHO-CLINICAL DIAGNOSTICS	VITROS IMMUNODIAGNOSTIC PRODUCTS ANTI-HBC REAGENT PACK/CALIBRATOR	P030024	3/4/2004	92.38% [89.46% - 94.70%]	99.60% [99.07% - 99.87%]
SIEMENS HEALTHCARE DIAGNOSTICS	ADVIA CENTAUR ANTI-HBS READYPACK REAGENTS AND CALIBRATORS	P030029	5/14/2004	92.8% [90.7% - 94.5%]	91.8% [90.2% - 93.3%]
SIEMENS HEALTHCARE DIAGNOSTICS	ADVIA CENTAUR HBC IGM READYPACK REAGENTS ADVIA CENTAUR HBC IGM QUALITY CONTROL MATERIALS	P030040	8/6/2004	40% [12.2% - 73.8%]	98.8% [98.2% - 99.2%]
SIEMENS HEALTHCARE DIAGNOSTICS	ADVIA CENTAUR HBC TOTAL READYPACK REAGENTS/ADVIA CENTAUR HBC TOTAL QUALITY CONTROL MATERIALS	P040004	12/22/2004	93.21% [91.21% - 94.88%]	96.43% [91.90% - 97.65]
ABBOTT LABORATORIES INC	AXSYM AUSAB	P060003	8/7/2006	92.11% [89.94% - 93.94%]	96.60% [95.44% - 97.54%]
ABBOTT LABORATORIES INC	AXSYM CORE-M 2.0 AND AXSYM CORE-M 2.0 CONTROLS	P060009	8/25/2006	100% [79.41% - 100.00%]	99.50% [[99.08% - 99.76%]
ABBOTT LABORATORIES INC	AXSYM CORE 2.0 AND AXSYM CORE 2.0 CONTROLS	P060012	9/8/2006	99.31% [97.54% - 99.92%]	97.45% [96.52% - 98.19%]

Bio-Rad Laboratories Inc.	BIO-RAD MONOLISA ANTI-HBC EIA	P060031	4/27/2007	97.8% [96%,9 - 8.8%]	95.5% [94% - 96.7%]
Bio-Rad Laboratories Inc.	BIO RAD MONOLISA ANTI-HBC IGM EIA	P060034	5/31/2007	91.7% [64.6% - 98.5%]	95.3% [94% - 96.3%]
Abbott Laboratories	ARCHITECT CORE-M REAGENT KIT/CALIBRATORS/CONTROLS	P060035	11/6/2007	96.77% [83.305 - 99.92%]	98.43% [97.73% - 98.96%]
Abbott Laboratories	ARCHITECT CORE REAGENT KIT ARCHITECT CORE CALIBRATOR AND ARCHITECT CORE CONTROLS	P080023	4/10/2009	97.64% [95.82% - 98.82%]	97.88% [96.98% - 98.56%]
ROCHE DIAGNOSTICS CORP.	ELECSYS ANTI-HBC IMMUNOASSAY & ELECSYS PRECICONTROL ANTI-HBC	P100031	6/22/2011	97.5% [95.2% - 98.9%]	98.2% [97% - 99.2%]
ROCHE DIAGNOSTICS CORP.	ELECSYS ANTI-HBC IMMUNOASSAY ELECSYS PRECICONTROL ANTI-HBC FOR USE ON THE ELECSYS 2010 IMMUNOASSAY ANALYZER	P100032	6/27/2011	Asympt. 97.60% [95.32% - 98.96%] Sympt. 98.08% [95.08% - 99.47%]	Asympt. 97.92% [96.47% - 98.89%] Sympt. 96.96% [94.63% - 98.47%]
ORTHO-CLINICAL DIAGNOSTICS	VITROS IMMUNODIAGNOSTIC PRODUCTS ANTI-HBE REAGENT PACK/ANTI-HBE CALIBRATOR/ANTI HBE CONTROLS	P100001	7/20/2011	97.74% [93.55% - 99.53%	100% [93.15% - 100%]
ROCHE DIAGNOSTICS CORP.	ELECSYS ANTI-HBC IGM IMMUNOASSAY AND ELECSYS PRECICONTROL ANTI-HBC IGM	P110022	10/26/2011	Asympt. 100% [69.15% - 100%] Sympt. 100% [39.76% - 100%]	Asympt. 100% [99.72%-100%] Sympt. 99.58% [97.70% - 99.99%]
ROCHE DIAGNOSTICS CORP.	ELECSYS ANTI-HBC IGM IMMUNOASSAY & ELECSYS PREICONTROL ANTI-HBC IGM FOR USE ON THE MODULAR ANAYTICS E170 IMMUNOASSAY ANA	P110025	12/14/2011	Asympt. 100% [63.1% - 100%] Sympt.100% [39.8% - 100%]	Asympt. 100% [99.7% - 100%] Sympt. 99.58% [97.7% - 99.99%]

ROCHE DIAGNOSTICS CORP.	ELECSYS ANTI-HBC IGM IMMUNOASSAY AND ELECSYS PRECICONTROL ANTI-HBC IGM	P110031	1/3/2012	Asympt. 100% [63.06% - 100.00%] Sympt. 100% [39.76% - 100%]	Asympt. 100% [99.72% - 100%] Sympt. 99.58% [97.70% - 99.99%]
DiaSorin Inc.	LIAISON XL MUREX Anti-HBc LIAISON MUREX Control Anti-HBc	P180038	1/2/2020	97.4%	98.8%
DiaSorin Inc.	LIAISON® XL MUREX anti-HBe LIAISON® XL MUREX Control anti-HBe	P180049	8/29/2020	98% [94.5% - 99.1%]	99.1% [98.7% - 99.4%]
DiaSorin Inc.	LIAISON® XL MUREX HBc IgM LIAISON® XL MUREX Control HBc IgM	P180045	8/29/2020	96.6% [92.2% - 98.5%]	98.8% [98.4% - 99.2%]
Roche Diagnostics	Elecsys Anti-HBe PreciControl Anti-HBe	P190005	2/3/2021	97.5% [94.2% - 99.2%]	95.1% [93.8% - 96.2%]
Siemens Healthcare Diagnostics Inc.	ADVIA Centaur Anti-HBe2 (aHBe2) assay	P200017	7/14/2021	XP: 97.6% [87.5%–96.2%] XPT; 92% [87.1%–95.2%] CP: 93.2% [88.5%–96.1%]	XP; 99% [98.4%–99.4%] XPT: 99.1% [98.5%–99.5%] CP; 99% [98.4%–99.4%]
Siemens Healthcare Diagnostics Inc.	ADVIA Centaur Anti-HBc Total (HBcT2) and Atellica IM Anti-HBc Total (HBcT2)	P210019	7/27/2022	XP: 98% [96.2%–98.9%] XPT: 98.2% [96.5%–99.1%] Atellica IM: 97.7% [95.9%–98.8%]	XP: 98.4% [97.4%–98.9%] XPT: 98.1% [97.1%–98.7%] Atellica IM: 98.6% [97.8%–99.1%]

*Overall PPA and NPA with their corresponding 95% CI. Note the overall PPA and NPA might not include the performance of the device in certain populations such as pregnant subjects and pediatrics.

When clinical study included samples collected and tested in the US and OUS, performance provided in this table is for samples collected and tested in the U

3. Table 3: Quantitative Hepatitis B surface antigen Antibody (Anti-HBs) Devices

Manufacturer	Device	PMA Number	Date of Approval	PPA [95% CI]*#	NPA [95% CI]*#
Siemens Healthcare Diagnostics Products LTD	IMMULITE 2000 XPI ANTI-HBS	P010052	7/22/2002	82.4% [83.2% - 97.5%]	97.2% [94% - 99%]
Abbott laboratories Inc	ABBOTT ARCHITECT AUSAB	P050051	6/1/2006	98.59% [97.42% - 99.32%]	96.68% [95.51% - 97.62%]
Bio-rad laboratories	MONOLISA ANTI-HBS EIA	P050048	8/25/2006	94.3% [92.2% - 95.9%]	93.5% [91.6% - 95.0%]
Siemens healthcare diagnostics Inc.	ADVIA CENTAUR ANTI-HBS2 (AHBS2) ASSAY AND QAULITY CONTROL MATERIAL	P100039	1/20/2012	97.9% [96.7% - 98.7%]	97.7% [96.7% - 98.5%]
DiaSorin Inc.	LIAISON® XL MUREX Anti-HBs LIAISON® XL MUREX Control Anti-HBs and LIAISON® XL MUREX Anti-HBs Verifiers	P180039	2/21/2020	97.4% [96.4% - 98.1%]	96.1% [95.0% - 97.0%]
Roche Diagnostics	Elecsys Anti-HBs II PreciControl Anti-HBs Anti-HBs CalCheck	P190034	2/23/2021	98.6% [97.6% - 99.3%]	96.5% [95.25% - 97.37%]

*Overall PPA and NPA with their corresponding 95% CI. Note the overall PPA and NPA might not include the performance of the device in certain populations such as pregnant subjects and pediatrics.

When clinical study included samples collected and tested in the US and OUS, performance provided in this table is for samples collected and tested in the U

4. Table 4: HBV Molecular Devices

Manufacturer	Device	PMA Number	Date of Approval	LoD* serum (IU/mL)	LoD* plasma (IU/mL)	Performance
Roche Molecular Systems Inc.	COBAS TAQMAN HBV TEST	P050028	9/4/2008	3.4	3.5	Refer to SSED summary

ABBOTT MOLECULAR INC.	ABBOTT REALTIME HBV ASSAY	P080026	8/13/2010	10 (0.5mL assay) 15 (0.2mL assay)	10 (0.5mL assay) 15 (0.2mL assay)	Refer to SSED summary
Roche Molecular Systems Inc.	COBAS HBV TEST	P150014	10/14/2015	2.4	2.7	Refer to SSED summary
Hologic Inc	Aptima HBV Quant Assay	P170025	1/23/2018	5.9	4.8	Refer to SSED summary
Abbott Molecular Inc.	Alinity m HBV	P200013	8/29/2020	10	10	Refer to SSED summary

*Values provided for LoD using the WHO International Standard. Refer to each Summary of Safety and Effectiveness for the LOD of each device in serum and plasma for different genotypes of the virus.

5. Table 5: Parvovirus Antibody Devices

Manufacturer	**Device**	**PMA Number**	**Date of Approval**	**PPA [95% CI)]**	**NPA [95% CI]**
DIASORIN	BIOTRIN PARVOVIRUS B19 IGG	P970054	8/6/1999	97.3%* [93.2-99.2]	96.1% [88.9-99.2]
DIASORIN	BIOTRIN PARVOVIRUS IGM EIA (V619IMUS)	P970055	8/6/1999	78.9%** [54.9-94.0]	96.1% [88.9-99.2]
ZEUS SCIENTIFIC, INC.	ZEUS ELISA PARVOVIRUS B19 IGM TEST SYSTEM	P150042	9/19/2017	91.1% # [82.8-99.4]	97.2% # [96.6-97.8]
ZEUS SCIENTIFIC, INC.	ZEUS ELISA PARVOVIRUS B19 IGG TEST SYSTEM	P150045	9/19/2017	99.3% # [98.9-99.7]	96.6% # [95.5-97.7]

* Overall PPA and corresponding 95% CI for the "previously infected, IgG+/IgM-" group.

** Overall PPA and corresponding 95% CI for the "Acute/Recent Infection IgG+/IgM+, IgG-/IgM+" patient groups.

#The overall PPA and NPA did not include the performance of the device in pregnant subjects.

6. Table 6: *M. tuberculosis* IGRA Devices

Manufacturer	**Device**	**PMA Number**	**Date of Approval**	**PPA [95% CI)]**	**NPA [95% CI]**
QIAGEN	QUANTIFERON-TB GOLD-IN-TUBE,	P010033	11/28/2001	88.7%* [77.4-94.7%]	99.06%** [96.63 – 99.74%]

	QUANTIFERON TB GOLD, QUANTIFERON-TB GOLD PLUS			81.0%* [69.2-89.1%] 88.7%* [77.4-94.7%]	99.2%** [97.65-99.8%] 98.11%** [95.25-99.26%]
OXFORD IMMUNOTEC, LTD.	T SPOT-TB TEST	P070006	7/30/2008	95.6%* [91.6-98.1%]	97.1%** [94.5-98.7%]
DiaSorin, Inc.	LIAISON QuantiFERON - TB Gold Plus, LIAISON Control QuantiFERON - TB Gold Plus and LIAISON QuantiFERON Software	P180047	11/26/2019	78.6%*, [69.77-85.45%]	96.9%** [94.2-98.3%]

* Estimated sensitivity as compared to culture confirmed TB disease

** Estimated specificity in subjects with low risk (no known risk factors) for tuberculosis infection