Introduction and Regulatory Reference Sheet
Microbiology Devices Panel
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
September 7, 2023

On September 7, 2023, the Microbiology Devices Panel (the panel) will discuss and make recommendations regarding the potential future reclassification of certain Class III infectious disease *in vitro* diagnostic devices (IVDs), including Hepatitis B Virus Antigen, Antibody, and Molecular Assays, (product codes LOM and MKT), Parvovirus Antibody Assays (product codes MYM and MYL), and *Mycobacterium tuberculosis* (TB) interferon gamma release assays (IGRA) (product codes NCD and OJN).

FDA is convening the Panel to help inform FDA's thinking regarding whether reclassification from Class III to Class II may be appropriate for such devices. Specifically, the Panel will consider whether there is sufficient information to establish special controls, in combination with general controls, for these devices.

At this meeting, the panel will be asked to discuss the classification 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,

2. Qualitative Parvovirus B19 antibody assays, and

3. Qualitative TB cell mediated immune reactivity/IGRA.

For each device type, the panel will discuss the indications for use, the risks to health, the available safety and effectiveness information, and the potential special controls.

After this panel meeting, the FDA will consider all available scientific evidence and the input from panel members in determining 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, could potentially be eligible for a Class II designation.

What data should be considered when making a classification recommendation?

Initial classification and reclassification decisions are based on existing information for legally marketed devices and their predicates. Although information on future technology or new indications applicable for these devices may be available, this information is not relevant to the deliberations of the panel. The panel must consider only the legally marketed cohort of each device type.

What are the definitions of Class I, Class II, and Class III?

Federal law (Federal Food, Drug, and Cosmetic Act, section 513), established the risk-based device classification system for medical devices. Each device is assigned to one of three regulatory classes: Class I, Class II or Class III, based on the level of control necessary to provide reasonable assurance of its safety and effectiveness.

As device class increases from Class I, to Class II to Class III, the regulatory controls also increase, with Class I devices subject to the least regulatory control, and Class III devices subject to the most stringent regulatory control.

The regulatory controls for each device class include:

- Class I (low to moderate risk): General Controls
- Class II (moderate to high risk): General Controls and Special Controls
- Class III (high risk): General Controls and Premarket Approval (PMA)

Class I, General Controls

A device is Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. Examples of general controls are registration and listing, medical device reporting, labeling and good manufacturing practices (GMPs). Devices may also be considered Class I if the device "is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury."[1] Most Class I devices including multipurpose culture medium devices are exempt from submitting a 510(k) and can be marketed without a premarket submission. Examples of Class I devices include elastic bandages, hand-held manual surgical instruments, and differential culture mediums.

Class II, Special Controls

A Class II device is "a device which cannot be classified as a Class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance."[2] Examples of special controls are: performance standards, post-market surveillance, patient registries, and special labeling requirements. Special controls may also include specific types of performance testing (e.g., analytical studies such as precision, interference, or limit of detection) or clinical studies using either prospectively collected samples or retrospective samples, which FDA may outline in the regulation. Most Class II devices require clearance of a 510(k) prior to marketing. Sponsors are required to submit valid scientific evidence in their 510(k) demonstrating that the device is as safe and effective as a predicate device. Companies submitting a 510(k) for a device must demonstrate how any specified special controls have been met in order to receive marketing clearance. Examples of Class II devices include intravascular administration sets (e.g., syringes), nucleic acid based IVDs for the detection of *Mycobacterium tuberculosis* complex, and endoscopes.

Class III, Premarket Approval

A Class III device is a device which:

1. "cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device," **and**
2. "cannot be classified as a class II device because insufficient information exists to determine that the special controls…would provide reasonable assurance of its safety and effectiveness," **and**
3. "is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health," **or**

[1] See Section 513(a)(1)(A) of the Food, Drug and Cosmetic (FD&C) Act.
[2] See Section 513(a)(1)(B) of the FD&C Act.

4. "presents a potential unreasonable risk of illness or injury."[3]

Class III devices require premarket approval prior to marketing the device and must provide valid scientific evidence to demonstrate that the device has demonstrated a reasonable assurance of safety and effectiveness through the submission of a PMA application. Examples of Class III devices include breast implants and Human Papillomavirus (HPV) diagnostic devices.

What will the panel be asked?

Risks to Health

The FDA will present the risks to health that they have identified to be associated with use of the device type. The panel will be asked to comment on whether they disagree with inclusion of any of the identified risks or whether they believe any other risks should be considered for this device type.

Special Controls

The panel will be asked to comment on whether any special controls can be identified to provide a reasonable assurance of safety and effectiveness in light of the available scientific evidence. If special controls can mitigate the identified risks to health, and safety and effectiveness have been established, it would be appropriate to recommend that this device type could potentially be classified into Class II, special controls.

What is a "reasonable assurance of safety"?

As defined in 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

What is a "reasonable assurance of effectiveness"?

As defined in 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

What are the practical implications of maintaining these infectious disease test types (qualitative HBV antigen assays, qualitative HBV antibody assays, quantitative assays that detect anti-HBs, quantitative HBV molecular assays, qualitative serology-based Parvovirus antibody assays, and qualitative TB cell mediated immune reactivity assays) as Class III?

If FDA chooses to maintain these test types (qualitative HBV antigen assays, qualitative HBV antibody assays, quantitative assays that detect anti-HBs, quantitative HBV molecular assays, qualitative serology-based Parvovirus antibody assays, and qualitative *Mycobacterium tuberculosis* cell mediated immune reactivity assays) in Class III, new devices or changes to existing devices would be subject to PMA review. Manufacturers of these test types

[3] See Section 513(a)(1)(C) of the FD&C Act.

would need to provide valid scientific evidence to demonstrate that the device has demonstrated a reasonable assurance of safety and effectiveness.

What happens if FDA decides to reclassify these infectious disease test types (qualitative HBV antigen assays, qualitative HBV antibody assays, quantitative assays that detect anti-HBs, quantitative HBV molecular assays, qualitative serology-based Parvovirus antibody assays, and qualitative TB cell mediated immune reactivity assays) into Class II?

If these devices are classified into Class II, these devices would become subject to the premarket notification [510(k)] requirements and any special controls specified in the final classification. Companies with existing legally marketed devices would be subject to the newly defined special controls and must ensure that their existing products meet all specified requirements. New devices and changes to existing devices that require a new submission to FDA would require a 510(k), demonstration that the special controls have been met, and a substantial equivalence (SE) determination.

What are the practical differences between PMA and 510(k) requirements?

A PMA application must provide all evidence to independently demonstrate a reasonable assurance of safety and effectiveness of the device. PMAs typically involve data from clinical trials of the specific device that support both safety and effectiveness, as well as detailed manufacturing information for the device. Conversely, a 510(k) submission can leverage existing information on predicate devices, including applicable clinical data, to support marketing clearance. For devices subject to 510(k), the premarket submission need only provide evidence that the device has indications and technological characteristics consistent with existing legally marketed predicate devices and meets any required special controls.

Once a PMA is approved, the PMA holder must report all design, manufacturing, and labeling changes made to the approved device to FDA via PMA supplements[4] and PMA annual reports[5]. PMA holders are also typically subject to ongoing post-market requirements. 510(k) holders are not subject to as stringent post-market oversight. For example, for 510(k) devices, companies do not need to submit many types of minor changes to a device or its labeling to FDA for review nor do they need to submit manufacturing changes or annual reports.

Regardless of the classification of these device types, FDA does not regulate the practice of medicine, specifically, which devices clinicians can use and how they use them.

[4] Refer to FDA's Guidance for Industry and FDA Staff: 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/30-day-notices-135- day-premarket-approval-pma-supplements-and-75-day-humanitarian-device-exemption).

[5] Refer to FDA's Guidance for Annual Reports for Approved Premarket Approval Applications (PMA) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/annual-reports-approved-premarketapproval-applications-pm