

FDA Executive Summary

Prepared for the
November 9, 2016 meeting of the
Microbiology Devices Panel of the
Medical Devices Advisory Committee

*Discussion and Recommendations for the Classification of
Quantitative Viral Load Assays for Transplant-associated
Opportunistic Viral Infections*

Gaithersburg, Maryland

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1. Introduction and Purpose of the Panel Meeting

The Division of Microbiology Devices (DMD) in the Office of In Vitro Diagnostics and Radiological Health (OIR), 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 Advisory Panel meeting to discuss and make recommendations regarding transplant-associated opportunistic viral infections.

The purpose of this meeting is to (1) discuss the reclassification of quantitative CMV viral load devices, currently regulated as Class III (premarket approval) devices, into Class II (510(k)), and (2) discuss the appropriate initial classification of quantitative viral load devices for EBV and BKV infections in patients immunocompromised due to solid organ or stem cell transplantation. FDA is seeking expert advice to determine the appropriate classification of these assays, and to discuss the risks and benefits of quantitative viral load assays to support and guide the development of special controls for analytes determined to be eligible for a Class II designation. The morning and early afternoon of November 9, 2016, will be reserved for discussion of reclassification of CMV viral load assays; the remainder of the day will be a general discussion of the benefits and risks of assays for EBV and BK virus as models for opportunistic transplant-associated viral infections.

In vitro diagnostic devices (IVD(s)) classified into Class III generally have greater FDA oversight and regulatory requirements than Class II devices. During the meeting, the Microbiology Devices 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, it may become apparent that reclassification is not appropriate at this time or, alternatively, that Special Controls can be developed such that safety and effectiveness is assured without the oversight required with Class III status and that FDA should pursue the reclassification process.

2. Background

a. Regulation of *In Vitro* Diagnostic Devices

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 *in vitro* diagnostic devices 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 original Federal Food, Drug and Cosmetic Act (FD&C Act).

(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/>). Medical devices, including *in vitro* diagnostic devices, are classified on the basis of risk. 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 risk for which general controls are sufficient to provide a reasonable assurance of safety and effectiveness of the device.
- Class II: Devices which require both general and special controls to provide a reasonable assurance of safety and effectiveness of the device.
- Class III: Devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the 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. Class I devices may also be devices that do not present a potential unreasonable risk of illness or injury.

General controls are controls not unique to any specific device but controls that can be applicable to devices in general. Examples of general controls include:

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

¹ All citations or references to the Code of Federal Regulations in this document are available at: <https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR>.

- That provide for notification of risks and of repair, replacement, or refund;
- Restrictions on sale and distribution or use; and
- Other regulatory controls, e.g., labeling, adverse event reporting, misbranding, adulteration of the device.

For example, multipurpose culture medium is a Class I device 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.

Due to their low risk, FDA has exempted almost all Class I devices (with the exception of reserved devices (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/3151.cfm>)) from the 510(k) requirement, including those devices that were exempted by final regulation published in the Federal Registers of December 7, 1994, and January 16, 1996. If a manufacturer's device falls into a generic category of exempted Class I devices, then a 510(k) submission and FDA clearance are not required before marketing the device in the United States. However, these devices have not been exempted from other general controls (e.g., registration and listing, GMP regulations, etc.).

Further all devices exempt from the premarket notification requirement are only exempt as long as they do not exceed the limitations to their exemption. Limitations to exemptions for microbiology devices are found in 21 CFR 866.9. Of these limitations on exemptions, an exemption especially relevant to many of microbiology diagnostic devices is if the device is intended “[f]or identifying or inferring the identity of a microorganism directly from clinical material” (21 CFR 866.9(c)(6)), as many of them are intended to be used directly from clinical specimens.

Further, although all manufacturers of medical devices are subject to the Quality System Regulation (21 CFR part 820), FDA has exempted almost all Class I devices (with the exception of five types of devices listed in 820.30(a)(2), none of which are *in vitro* diagnostic devices) from the design controls requirement. The intent of the design controls regulation is to implement processes and procedures to allow for identifying deficiencies in the design input requirements in early stages of the development of a device and it also applies to all changes to

the device or manufacturing process design, including those occurring long after a device has been introduced to the market. These changes are part of a continuous, ongoing effort to design, develop and make available a device that meets the needs of the user and/or patient.

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. Examples of special controls may include:

- performance standards;
- post-market surveillance;
- patient registries;
- guidelines; and
- other appropriate action deemed necessary for mitigating the risks of the device.

For example, a culture medium intended to determine whether a particular organism is susceptible to a drug that can be used to treat a bacterial infection is a Class II device as specified in the Code of Federal Regulations:

21 CFR 866.1700 Culture medium for antimicrobial susceptibility tests.

(a) *Identification.* A culture medium for antimicrobial susceptibility tests is a device intended for medical purposes that consists of any medium capable of supporting the growth of many of the bacterial pathogens that are subject to antimicrobial susceptibility tests. The medium should be free of components known to be antagonistic to the common agents for which susceptibility tests are performed in the treatment of disease.

(b) *Classification.* Class II (performance standards).

Class I reserved (non-exempt) and Class II submissions are reviewed by FDA under what is referred to as the 510(k) process. Under the 510(k) paradigm, a device can be cleared for marketing if it is determined to be as safe and effective as a preexisting ‘predicate’ device (the device is ‘substantially equivalent’ to the predicate device).² Substantial equivalence broadly encompasses the following:

- The new device has the same intended use as the predicate and the new device has the same technological characteristics as the predicate,
- **or**
- The new device has the same intended use as the predicate but the new device has different technological characteristics and the information submitted to FDA *and* the

² 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.

device both (a) does not raise new questions of safety and effectiveness and (b) the sponsor demonstrates that the device is at least as safe and effective as the legally marketed device.

As described on the FDA web site, “a claim of substantial equivalence does not necessarily imply that the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.” The determination of ‘substantial equivalence,’ is therefore a multifaceted examination of the new device focused heavily on the intended use and not independent of the underlying technology.³

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 sustaining or life supporting, of substantial importance in preventing impairment of human health, or present unreasonable risk of illness or injury. Class III devices require ‘pre-market approval’ (PMA) applications for which additional materials are necessary at the time of regulatory filing by the sponsor/manufacturer and FDA has greater oversight over Class III than over Class II and Class I devices.⁴

b. Current Regulation of Quantitative CMV Viral Load Assays

FDA currently regulates quantitative CMV viral load assays as *in vitro* nucleic acid-based prescription diagnostic devices intended for use as an aid in the management of transplant patients to measure CMV DNA in human plasma using specified specimen processing, amplification, and detection instrumentation. The test is intended for use as an aid in the management of transplant patients with active CMV infection or at risk for CMV infection. Test results must be interpreted in conjunction with other relevant clinical and laboratory findings. At present there are two marketed CMV viral load assays, and each has an intended use similar to the following:

³ More detailed information regarding pre market applications under the 510(k) process is available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>, reproduced as an attachment to this document.

⁴ More detailed information regarding pre market PMA applications is available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>, reproduced as an attachment to this document.

The [CMV Assay] is an *in vitro* nucleic acid amplification test for the quantitative measurement of cytomegalovirus (CMV) DNA in human EDTA plasma using the [CMV Instrument] for automated specimen processing and the [Analyzer] for automated amplification and detection.

The [CMV Assay] is intended for use as an aid in the management of solid-organ transplant patients who are undergoing anti-CMV therapy. In this population serial DNA measurements can be used to assess virological response to antiviral treatment. The results from the [CMV Assay] must be interpreted within the context of all relevant clinical and laboratory findings.

The [CMV Assay] Test is not intended for use as a screening test for the presence of CMV DNA in blood or blood products.

FDA currently regulates CMV viral load assays as Class III devices requiring PMA applications. The subject of the November 9, 2016, meeting is to seek advice and recommendations from the committee regarding whether nucleic acid-based *in vitro* diagnostic devices for the quantitation of CMV viral load can be reclassified into Class II on the basis that there is sufficient information to establish special controls, in addition to general controls, to provide a reasonable assurance of the safety and effectiveness of the device. There will be further discussion of the nature of special controls at the panel meeting.

3. The Clinical Setting of CMV Infection

In the post-transplantation setting, CMV infection and CMV disease are significant sources of morbidity and mortality following all types of solid-organ (SOT) and hematopoietic stem cell transplantation (HSCT). The CMV Drug Development Forum has recently recommended updated definitions of CMV infection in clinical trials to allow for more consistent evaluation of clinical trials for treatment of CMV. In their report⁵, CMV infection is defined as, “virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen. It is recommended that both the source of the specimens tested (e.g., plasma, serum, whole blood, peripheral blood leukocytes (PBL), cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL) fluid, urine, or tissue) and the diagnostic method used be described.” The

⁵ Ljungman, P., et al. (2016). "Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials." *Clinical Infectious Diseases* .

American Society of Transplantation similarly differentiates between CMV infection and disease by the presence of clinical signs and symptoms such as the following⁶:

- CMV infection: evidence of CMV replication regardless of symptoms (differs from latent CMV).
- CMV disease: evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as a viral syndrome with fever, malaise, leukopenia, and/or thrombocytopenia or as tissue-invasive disease.

Typical symptoms associated with ‘CMV syndrome’ include fever, malaise, gastrointestinal discomfort, leukopenia and thrombocytopenia whereas more severe clinical manifestations such as pneumonitis, hepatitis, pancreatitis meningoencephalitis and myocarditis are suggestive of CMV tissue-invasive disease. CMV end-organ disease can occur in a variety of different organs including the liver, lung, pancreas and gastrointestinal tract, but requires documentation of CMV on tissue histopathology, viral isolation from biopsy, immunohistochemistry or DNA hybridization techniques to meet criteria for proven disease.

All patients immunosuppressed post-transplant are at risk for the development of CMV disease, although absolute risk varies substantially within well-defined subgroups. For instance, relative to SOT, patients following hematopoietic stem cell transplantation (HSCT) are a particularly fragile population in which between 50% to 80% of patients develop CMV viremia following bone marrow transplant and where prophylaxis is not routinely used due to drug toxicity. There is nearly 25% mortality within 1 year post transplant in those that develop CMV end organ disease. For both groups, the decision to use prophylaxis or treat with anti-CMV therapy is a benefit/risk decision, based on all available clinical and laboratory findings and considering known toxicities from anti-CMV therapy, particularly bone marrow suppression.

The onset of CMV infection most frequently occurs between days 30 and 90 following solid-organ transplantation in patients not receiving CMV prophylaxis, but may occur earlier in HSCT-recipients. The presence of CMV viremia is used as a precursor to potentially significant infection, and is closely monitored to prevent the development and damaging effects of CMV disease using one or more detection methods. The preferred method and current standard of care for detecting CMV viremia diagnosis is by molecular methods, specifically real-time quantitative NAATs. CMV NAAT assays are generally faster with higher throughput and less subjectivity than the antigenemia assays; however, different CMV NAATs may utilize different genomic targets, probes and extraction protocols, and as a result may exhibit poor inter-laboratory correlation.

⁶ Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, Humar A; Transplantation Society International CMV Consensus Group. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*. 2013;96(4):333-60.

Most transplantation centers managing CMV viremia/infection have deep familiarity with the quantitative tests for CMV viral load used at their facility. In many cases this reflects long clinical experience with site specific tests such that patient risk from use of these tests is minimized. However, with increasing decentralization of patient care, potential discrepancies between results from different assays may lead to a different interpretation than if the same assay were used.

While monitoring of CMV viremia in patient plasma or whole blood plays an important role in early CMV detection and viral load monitoring in response to treatment, the use of prophylaxis post-transplantation is influenced by the patient's risk of developing CMV infection. Factors considered in addition to transplant type (among others) are pre-transplant serological status, host donor mismatch, immunosuppressive regimen, immunological status during the post-transplant period, and potential use of preemptive monitoring; for example, Patients at the highest risk of developing post-transplant CMV infection are those who test CMV IgG negative (R-) and whose donor tests CMV IgG positive (D+). All other combinations, with the exception of D-/R- (low risk), are considered to pose an intermediate risk of CMV infection to the recipient. Assessment of patient immunological status by T cell reactivity is an area of ongoing investigation that also may add to predicting risk of CMV infection post-transplant. In all cases, the decision regarding how to approach a patient post-transplant or with low-level DNAemia fundamentally rests on the benefit/risk assessment by the transplant team, considering all available clinical and laboratory findings and considering known toxicities from anti-CMV therapy, particularly bone marrow suppression.

Due to differences between assays, particularly the use of either FDA-approved and laboratory developed tests at different clinical centers, viral load cut-off values to reliably distinguish between possible, probable and proven CMV disease have not been established. Variability in test performance across different laboratories has been well documented; to reduce interlaboratory variability and address the need for the establishment of consistent viral load measurement for clinical decision making, the World Health Organization recently released an International Reference Standard (WHO IS) for use with CMV NAATs. Studies have shown that although standards such as the WHO IS improve the commutability of test results, i.e., results from measurement of the standard must show the same measurement in patient results, showing the same absolute result, this does not fully address all concerns that may be expected from variability across quantitative assays⁷. This will be discussed further at the panel meeting.

⁷ Preiksaitis JK, Hayden RT, Tong Y, et al. Are we there yet? Impact of the 1st International Standard for cytomegalovirus DNA on the harmonization of results reported on plasma samples. Clin Infect Dis 2016; 63:583–9.

4. Risks to Health:

When considering possible reclassification of any FDA-regulated device, FDA considers the risks to health. In consideration of the significant health impact that that CMV end organ disease presents to patients and the important role of CMV viral measurement in mitigating disease, the following specific risks, while not meant to represent all risks associated with CMV viral load measurement, would appear to be some of the major concerns that would need to be addressed:

- a. An inaccurate low test result, or false negative result, may lead to inappropriate patient management decisions such as a premature discontinuation of antiviral therapy or withholding of therapy, which can lead to serious injury including death.
- b. An inaccurate high test result, or a false positive result, may contribute to unnecessary initiation of treatment, a change in therapy, prolonged duration of therapy which could potentially result in serious adverse events.
- c. Variability across different devices may lead to different clinical decisions, e.g., a less sensitive test could lead to earlier discontinuation of treatment, even if performing appropriately. With increasing decentralization of treatment and restrictions on test selection, there is increased risk of patients being exposed to measurements of CMV viral load by tests from different sources.

5. Special Controls:

We anticipate robust discussion of Special Controls at the panel meeting. Possible considerations could include:

- a. Limitations 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 that the tests is intended to be used in conjunction with the patient's medical history, clinical signs and symptoms, and results from other relevant laboratory findings.
- b. Analytical method comparison studies to demonstrate the estimated systematic differences between the device and both the WHO standard and an FDA accepted comparator method. These studies would include predefined maximum allowable total difference (ATD) zones between the new assay and comparator test material. A maximum deviation from linearity would also be redefined.
- c. Clinical studies similarly confirming acceptable performance relative to assays previously granted marketing authorization by FDA, particularly at clinically significant values but also across the entire measurement range.
- d. Commutability with the WHO standard

Test manufacturers would need to comply with the specific mitigation measures set forth in the special controls.

6. Questions:

- a. Do committee members believe that special controls, in addition to general controls, are necessary and sufficient to mitigate the risks to health presented by quantitative CMV viral load assays?
 - In addressing this question, please discuss the specific special controls that would be recommended if reclassification could be considered for quantitative CMV viral load assays.

7. Appendix: Definitions of CMV infection

CMV Infection: “CMV infection” is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen. It is recommended that both the source of the specimens tested (e.g., plasma, serum, whole blood, peripheral blood leukocytes (PBL), cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL) fluid, urine, or tissue) and the diagnostic method used be described clearly.

CMV Replication: The term replication can be used to indicate evidence of viral multiplication and is sometimes used instead of CMV infection.

Primary CMV Infection: Primary CMV infection" is defined as the first detection of CMV infection in an individual who has no evidence of CMV exposure before transplantation. It is recognized that severely immunocompromised individuals such as transplant patients might not develop CMV specific antibodies.

Recurrent CMV Infection: “Recurrent infection” is defined as new CMV infection in a patient with previous evidence of CMV infection, which has not had virus detected for an interval of at least 4 weeks during active surveillance. Recurrent infection may result from reactivation of latent virus (endogenous) or reinfection (exogenous). It is recognized that CMV specific antibodies can be passively transferred by blood products or immune globulin administration. For practical purposes, presence or absence of CMV specific antibodies by serology can be used as acceptable estimates of previous CMV exposure to classify patients for entry into clinical trials.

CMV Reinfection. “Reinfection” is defined as detection of a CMV strain that is distinct from the strain that caused the initial infection.

CMV Reactivation. CMV reactivation is likely if the 2 viral strains (prior and current strain) are found to be indistinguishable either by sequencing specific regions of the viral genome or by using a variety of molecular techniques that examine genes known to be polymorphic

CMV detection in blood

Several specific definitions for CMV detection in blood are recommended. It should be noted that evidence suggests that the detection of virus, antigen, or DNA in blood does not mean that CMV is replicating in blood.

Viremia. “Viremia” is defined as the isolation of CMV by either standard or rapid culture techniques. These techniques are, however, rarely used today for monitoring of transplant recipients

Antigenemia. “Antigenemia” is defined as the detection of CMV pp65 antigen in PBL.

DNAemia. “DNAemia” is defined as the detection of CMV DNA in samples of plasma, serum, whole blood, isolated PBL or in buffy-coat specimens. There are several techniques available for the detection and quantitation of CMV DNAemia. It is strongly recommended that the nucleic acid amplification techniques have been calibrated to a standard calibrator, such as the WHO International Standard for Human CMV [6].

RNAemia. “RNAemia” is defined as the detection of CMV RNA in samples of plasma, serum, whole blood, isolated PBL or in buffy-coat specimens. These techniques are not commonly used for monitoring of transplant patients despite having the theoretical advantage of documenting transcription of the genome sequence.