



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2016-N-2880]

Microbiology Devices; Reclassification of Cytomegalovirus Deoxyribonucleic Acid Quantitative Assay Devices Intended for Transplant Patient Management, To Be Renamed Quantitative Cytomegalovirus Nucleic Acid Tests for Transplant Patient Management

AGENCY: Food and Drug Administration, HHS.

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

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to reclassify cytomegalovirus (CMV) deoxyribonucleic acid (DNA) quantitative assay devices intended for transplant patient management, a postamendments class III device (product code PAB) into class II (general controls and special controls), subject to premarket notification. FDA is also proposing a new device classification regulation with the name "quantitative cytomegalovirus (CMV) nucleic acid tests for transplant patient management" to identify these devices along with the special controls that the Agency believes are necessary to provide a reasonable assurance of safety and effectiveness for the device. FDA is proposing this reclassification on its own initiative. If finalized, this order will reclassify these types of devices from class III (general controls and premarket approval) to class II (general controls and special controls) and reduce the regulatory burdens associated with these devices as manufacturers of these types of devices will no longer be required to submit a premarket approval application

(PMA), but can instead submit a premarket notification (510(k)) and obtain clearance, before marketing their device.

**DATES:** Submit either electronic or written comments on the proposed order by [INSERT 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Please see section XII of this document for the proposed effective date when the new requirements apply and for the proposed effective date of a final order based on this proposed order.

**ADDRESSES:** You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

#### *Electronic Submissions*

Submit electronic comments in the following way:

- **Federal Rulemaking Portal:** <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing

process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed below (see "Written/Paper Submissions" and "Instructions").

#### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions:* All submissions received must include the Docket No. FDA-2016-N-2880 for "Microbiology Devices; Reclassification of Cytomegalovirus Deoxyribonucleic Acid Quantitative Assay Devices Intended for Transplant Patient Management, To Be Renamed Quantitative Cytomegalovirus Nucleic Acid Tests for Transplant Patient Management." Received comments, those filed in a timely manner (see ADDRESSES) will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Silke Schlottmann, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3258, Silver Spring, MD 20993-0002, 301-796-9551, Silke.Schlottmann@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

### I. Background--Regulatory Authorities

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

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices) are automatically classified by section 513(f)(1) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless and until: (1) FDA reclassifies the device into class I or class II or (2) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. FDA determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807), subpart E, of FDA's regulations.

A postamendments device that has been initially classified in class III under section 513(f)(1) of the FD&C Act may be reclassified into class I or II under section 513(f)(3) of the FD&C Act. Section 513(f)(3) of the FD&C Act provides that FDA, acting by administrative

order, can reclassify the device into class I or class II on its own initiative, or in response to a petition from the manufacturer or importer of the device. To change the classification of the device, the proposed new class must have sufficient regulatory controls to provide a reasonable assurance of the safety and effectiveness of the device for its intended use.

FDA relies upon "valid scientific evidence," as defined in section 513(a)(3) of the FD&C Act and 21 CFR 860.7(c)(2), in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the "valid scientific evidence" upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA application (see section 520(c) of the FD&C Act (21 U.S.C. 360j(c))).

In accordance with section 513(f)(3) of the FD&C Act, FDA is issuing this proposed order to reclassify CMV DNA quantitative assay devices intended for transplant patient management, postamendments class III devices, into class II (general controls and special controls), subject to premarket notification because FDA believes the standard in section 513(a)(1)(B) of the FD&C Act is met as there is sufficient information to establish special controls, which in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device.<sup>1</sup>

Section 510(m) of the FD&C Act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the FD&C Act, if the Agency

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<sup>1</sup> In December 2019, FDA began adding the term "Proposed amendment" to the "ACTION" caption for these documents, typically styled "Proposed order", to indicate that they "propose to amend" the Code of Federal Regulations. This editorial change was made in accordance with the Office of Federal Register's interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

determines that premarket notification is not necessary to reasonably assure the safety and effectiveness of the device. FDA has determined that premarket notification is necessary to reasonably assure the safety and effectiveness of CMV DNA quantitative assay devices intended for transplant patient management. Therefore, the Agency does not intend to exempt these proposed class II devices from premarket notification (510(k)) submission as provided under section 510(m) of the FD&C Act.

## II. Regulatory History of the Device

In accordance with section 513(f)(1) of the FD&C Act, CMV DNA quantitative assay devices intended for transplant patient management were automatically classified into class III because they were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, and have not been found substantially equivalent to a device placed in commercial distribution after May 28, 1976, which was subsequently classified or reclassified into class II or class I. Therefore, the device is subject to PMA requirements under section 515 of the FD&C Act (21 U.S.C. 360e).

Accordingly, on July 5, 2012, the Center for Devices and Radiological Health approved its first CMV DNA quantitative assay for the quantitative measurement of CMV DNA in human ethylenediaminetetraacetic acid plasma for use as a prescription device as an aid in the management of transplant patients, through its PMA process under section 515 of the FD&C Act. In the January 7, 2013, *Federal Register* (78 FR 950) notice, FDA announced the PMA approval order for the first CMV DNA quantitative device (Roche Molecular Systems, Inc's COBAS AmpliPrep/COBAS TaqMan CMV Test) and the availability of the Summary of Safety and Effectiveness Data (SSED) for the device.

Since this first approval order, FDA has approved three additional original PMA applications for CMV DNA quantitative assay devices intended for transplant patient management that are prescription devices intended for use, by a qualified licensed healthcare professional in conjunction with other relevant clinical and laboratory findings, in the detection of CMV and as an aid in the management of transplant patients with active CMV infection or at risk of developing CMV infection by measuring CMV DNA levels in human plasma and/or whole blood using validated specimen processing, amplification, and detection instrumentation (hereafter referred to as "CMV transplant assays.") These are prescription devices that are assigned the product code PAB. As of the date of this proposed order, the Agency has not received any recalls for these devices and has seen a relatively low incidence of Medical Device Reports (MDRs).

Based on a review of the MDR database, five MDRs have been received for the original Roche Molecular Systems, Inc's COBAS AmpliPrep/COBAS TaqMan CMV Test. These MDRs included one MedWatch report in 2015 describing a high false positive rate during performance verification, one adverse event reported to FDA in May of 2014 for the overquantitation of CMV, and three adverse events reported to FDA between December 2015 and February 2017 for the underquantitation of CMV. Evaluation of the patient samples from the 2015 and 2017 adverse event reports revealed mismatches between the assay primers and patient CMV sequences. Three additional MDRs were received between 2018 to 2019 for the ABBOTT Realtime CMV. All three adverse events were reports of overquantification of CMV viral load and none of these reported adverse events were associated with patient injury.

These adverse events reflect the risks to health FDA identified in section VI, and FDA believes the special controls proposed, in addition to general controls, can effectively mitigate the risks identified in these adverse event reports.

### III. Device Description

CMV transplant assays are postamendment prescription devices for transplant patient management and are devices classified into class III under section 513(f)(1) of the FD&C Act. These devices are described in FDA SSEDs and in the product code database (assigned product code PAB) as in vitro nucleic acid assays for the quantitative measurement of CMV DNA in human plasma or whole blood. The assay can be used to measure CMV DNA levels serially at baseline and during the course of antiviral treatment to assess virological response to treatment. The test results are to be interpreted within the context of all relevant clinical and laboratory findings.

FDA is proposing to reclassify CMV transplant assays from class III (general controls and premarket approval) to class II (general controls and special controls) and change the device type name to quantitative CMV nucleic acid tests for transplant patient management. FDA believes that the following description most accurately describes this device type and proposes its use for these types of devices. A quantitative CMV nucleic acid test for transplant patient management is tentatively identified as a device intended for prescription use in the detection of CMV and as an aid in the management of transplant patients to measure CMV DNA levels in human plasma and/or whole blood using validated 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 developing CMV infection. The test results are intended to be interpreted by a qualified licensed healthcare professional in conjunction with

other relevant clinical and laboratory findings. A condition defined as the isolation of virus or detection of viral proteins or viral nucleic acid in any body fluid or tissue specimen (Ref. 1). CMV infection in the setting of solid organ transplant or hematopoietic stem cell transplantation has previously been associated with significant patient morbidity, including organ rejection, end organ disease and death (Ref. 2). Currently, CMV transplant assays are used as an aid in the management of transplant patients with active CMV infection or at risk of developing CMV infection. The introduction of quantitative CMV nucleic acid tests for transplant patient management into clinical practice has helped to reduce the overall rates of CMV-associated morbidity and mortality post-transplant by enabling detection and quantification of CMV DNAemia (the presence of CMV DNA in blood or plasma) in patients, and accordingly, earlier intervention when necessary. CMV transplant assays are also used to assess patient response during antiviral treatment in order to guide management decisions.

Healthcare professionals managing transplant patients with CMV DNAemia or CMV infection often have substantial clinical experience with quantitation of CMV DNA such that patient risks are reduced when these tests are used for clinical management. Based upon our review experience and consistent with the FD&C Act and FDA's regulations, FDA believes that these devices should be reclassified from class III into class II because there is sufficient information to establish special controls that, along with general controls, can provide reasonable assurance of the devices' safety and effectiveness.

#### IV. Proposed Reclassification

FDA is proposing to reclassify CMV transplant assay devices. On November 9, 2016, the Microbiology Devices Panel (Panel) of the Medical Devices Advisory Committee convened to discuss and make recommendations regarding the reclassification of CMV transplant assays

from class III (general controls and premarket approval) into class II (general controls and special controls). Panel members unanimously agreed that special controls, in addition to general controls, are necessary and sufficient to mitigate the risks to the health of transplant patients presented by these devices (Ref. 4).

FDA agrees and believes that at this time, sufficient data and information exist such that the risks identified in section VI can be mitigated by establishing special controls that, together with general controls, can provide a reasonable assurance of the safety and effectiveness of these devices and therefore proposes these devices be reclassified from class III (general controls and premarket approval) to class II (general controls and special controls).

In accordance with section 513(f)(3) of the FD&C Act and 21 CFR part 860, subpart C, FDA is proposing to reclassify postamendments CMV transplant assays to be renamed "quantitative CMV nucleic acid tests for transplant patient management," from class III into class II. FDA believes, at this time, that there is sufficient data and information available to FDA through FDA's accumulated experience with these devices from review submissions, recommendations provided by professional organizations, and from published literature, as well as the recommendations provided by the Panel, to demonstrate that the proposed special controls, along with general controls, would effectively mitigate the risks to health identified in section VI and provide a reasonable assurance of safety and effectiveness of these devices. Absent the special controls identified in this proposed order, general controls applicable to the device type are insufficient to provide reasonable assurance of the safety and effectiveness of these devices. FDA expects that the reclassification of these devices would enable more manufacturers to develop quantitative CMV nucleic acid tests for transplant patient management such that patients would benefit from increased access to safe and effective tests.

FDA is proposing to create a classification regulation for quantitative CMV nucleic acid tests for transplant patient management that will be reclassified from class III to class II. Under this proposed order, if finalized, quantitative CMV nucleic acid tests for transplant patient management will be identified as a prescription device as these prescription devices require the supervision of a practitioner licensed by law to direct the use of the device in order to ensure accurate interpretation of results and so that these devices will provide a reasonable assurance of safety and effectiveness. As such, the prescription device must satisfy prescription labeling requirements for in vitro diagnostic products (see 21 CFR 809.10(a)(4) and (b)(5)(ii)). In this proposed order, if finalized, the Agency has identified the special controls under section 513(a)(1)(B) of the FD&C Act that, together with general controls, will provide a reasonable assurance of the safety and effectiveness for quantitative CMV nucleic acid tests for transplant patient management devices.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For quantitative CMV nucleic acid tests for transplant patient management, FDA has determined that premarket notification is necessary to provide a reasonable assurance of the safety and effectiveness of these devices. Therefore, FDA does not intend to exempt these proposed class II devices from the 510(k) requirements. If this proposed order is finalized, persons who intend to market this type of device must submit a 510(k) to FDA and receive clearance prior to marketing the device.

This proposed order, if finalized, will decrease regulatory burden on industry, as manufacturers will no longer have to submit a PMA application for these types of devices but

can instead submit a 510(k) to the Agency for review prior to marketing their device. A 510(k) typically results in a shorter premarket review timeline compared to a PMA application, which ultimately provides more timely access of these types of devices to patients.

In addition, the Agency believes that certain changes could be made to quantitative CMV nucleic acid tests for transplant patient management that could significantly affect the safety and effectiveness of those devices and for which a new 510(k) is likely required.<sup>2</sup> Based on FDA's accumulated experience with these devices, changes that likely could significantly affect the safety and effectiveness of these devices include, but are not limited to, changes to critical reagents, changes to final release specifications, and changes in shelf life of the device. For more information about when to submit a new 510(k), manufacturers should refer to FDA's guidance entitled "Deciding When to Submit at 510(k) for a Change to an Existing Device" (Ref. 3).

## V. Risks to Health

The incidence of CMV infection among transplant patients is highly variable and is dependent upon multiple factors, most importantly the serostatus of the donor/recipient pair, the type of transplant the patient received, and the recommended course of immunosuppressive therapy. If left untreated, transplant patients with CMV infection have significant risk of developing severe CMV-associated diseases, including gastroenteritis, pneumonia, hepatitis, pancreatitis, and myocarditis. However, the risk of CMV-associated morbidity and mortality has been considerably lowered with effective post-transplant prophylactic and preemptive antiviral

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<sup>2</sup> See 21 CFR 807.81(a)(3)(i).

treatments, combined with the use of quantitative CMV nucleic acid tests for transplant patient management as part of the current standard monitoring practices.

After consideration of FDA's accumulated experience with these devices from review submissions, the recommendations provided by professional organizations, the recommendations of the Panel for the classification of these devices (Ref. 4), and published literature, FDA has identified the following probable risks to health associated with quantitative CMV nucleic acid tests for transplant patient management:

- *Inaccurate interpretation of test results.* Inaccurate interpretation of test results by clinicians may lead to misdiagnosis with potentially significant impact on patient management.
- *Risk of false results (inaccurately low or false negative test result and inaccurately high or false positive test results).* An inaccurately low or false negative test result may cause withholding or discontinuation of antiviral therapy which can lead to serious injury, including death. An inaccurately high or false positive test result could lead to the unnecessary initiation of treatment, a change in therapy and/or prolonged duration of therapy, and increased patient risk to the potential adverse effects of CMV antiviral medications.
- *Decreased test sensitivity and/or increased rates of false negative test reporting.* Decreased test sensitivity and/or increased rates of false negative test reporting may occur with patient samples containing high CMV strain variability, de novo mutations in genomic regions of CMV targeted by the device, or undetectable CMV in the peripheral blood which can occur in CMV infected patients with tissue invasive disease. Increased

rates of false negative test reporting due to drift in accuracy due to changes in the viral genomic target may also pose significant risks to patient health.

- *Variability in CMV viral load measurement across different devices.* Variability in CMV viral load measurement across different devices may influence patient management decisions (e.g., a less sensitive test could lead to earlier discontinuation of treatment), even if performed appropriately.

## VI. Summary of the Reasons for Reclassification

FDA believes that quantitative CMV nucleic acid tests for transplant patient management should be reclassified from class III (general controls and premarket approval) into class II (general controls and special controls) because special controls, in addition to general controls, can be established to mitigate the risks to health identified in section VI and provide a reasonable assurance of the safety and effectiveness of these devices. The proposed special controls are identified by FDA in section VII.

Taking into account the probable health benefits of the use of these devices and the nature and known incidence of the risks of the devices, FDA, on its own initiative, is proposing to reclassify these postamendments class III devices into class II. FDA believes that, when used as indicated, quantitative CMV nucleic acid tests for transplant patient management can provide significant benefits to clinicians and patients, including guiding therapeutic intervention in the setting of CMV DNAemia and assessment of virological response to anti-CMV therapy.

FDA's reasons for reclassification are based on the scientific and medical information available regarding the nature, complexity, and risks associated with quantitative CMV nucleic acid tests for transplant patient management. The safety and effectiveness of this device type has become well established since the initial approval of the first CMV transplant assay in 2012.

Quantitative CMV nucleic acid tests for transplant patient management have been used for clinical management of transplant patients nationally and internationally for many years. The Transplantation Society International CMV Consensus Group has published recommendations that serve to standardize the clinical practice for CMV viral load measurement in the context of transplant patient management (Ref. 5).

## VII. Proposed Special Controls

FDA believes that these devices can be classified into class II with the establishment of special controls. FDA believes that the following special controls, together with general controls will provide reasonable assurance of the safety and effectiveness of the device type, table 1 demonstrates how these proposed special controls will mitigate each of the risks to health identified in section VII.

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

The risk of false results (e.g., inaccurately low-test result or a false negative test result and inaccurately high-test result or false positive test result) can be mitigated through a combination of special controls including certain labeling requirements, certain design verification and validation information, and performance studies. Examples of labeling mitigations include certain warnings and limitations, as well as a detailed explanation of the interpretation of results and detailed explanation of principles of operation and procedures for the device. Required statements in the labeling can aid in mitigating the failure of the device to perform as indicated. Examples of verification and validation information to be included in the design of the devices includes documentation of performance specifications including analytical

and clinical design specifications and the use of appropriate data analysis methods for method comparison studies, and documentation of a complete device description, calibrators, critical reagents, traceability, lot release criteria, stability studies, and protocols.

The risk of decreased test sensitivity and/or increased rates of false negative test reporting can be mitigated by special controls related to certain labeling, design verification and validation activities, failure mode analysis, and performance studies.

Risks associated with test variability in CMV viral load measurement across different devices may influence patient management decisions and could lead to adverse effects on patient health. To mitigate such risks, new devices must be calibrated to an FDA acceptable standardized reference standard material determined by FDA to be an appropriate reference material and must demonstrate continued traceability to appropriate standardized reference materials. The risk attributable to variability between different manufacturers' devices may also be mitigated through specific warnings in the labeling.

This reclassification order and the identified special controls, if finalized, would provide sufficient detail regarding FDA's requirements to reasonably assure safety and effectiveness of quantitative CMV nucleic acid tests for transplant patient management.

Table 1.--Risks to Health and Mitigation Measures for Quantitative CMV Nucleic Acid Tests for Transplant Patient Management

Identified Risks to Health	Mitigation Measures
Inaccurate interpretation of test results	Certain labeling warnings, limitations, results interpretation information, and explanation of procedures
Risk of false results	Certain labeling warnings, limitations, results interpretation information, and explanation of procedures; Certain design verification and validation information, including documentation of device descriptions, calibrators, critical reagents, traceability, lot release criteria, stability studies and protocols, and documentation of analytical and clinical studies
Decreased test sensitivity and/or increased rates of false negative test reporting.	Certain labeling warnings, limitations, results interpretation information, and explanation of procedures; Certain design verification and validation information, including traceability, lot release criteria, risk analysis, device descriptions and specifications, analytical studies, and clinical studies

Variability in CMV viral load measurement across different devices	Certain results interpretation information in labeling; Certain design verification and validation information, including documentation of device descriptions and specifications, analytical studies, clinical studies, and traceability studies
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If this proposed order is finalized, quantitative CMV nucleic acid tests for transplant patient management will be reclassified into class II (general controls and special controls) and would be subject to premarket notification requirements under section 510(k) of the FD&C Act. As discussed below, the intent is for the reclassification to be codified in 21 CFR 866.3180. Firms submitting a premarket notification under section 510(k) of the FD&C Act for quantitative CMV nucleic acid tests for transplant patient management will be required to comply with the particular mitigation measures set forth in the special controls. Adherence to the special controls, in addition to the general controls, is necessary to provide a reasonable assurance of the safety and effectiveness of these devices.

#### VIII. Analysis of Environmental Impact

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

#### IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed order contains no new collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required. However, this proposed order refers to previously approved collections of information. These collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910-0120, the collections of information in 21 CFR part 820 have been approved under OMB control number

0910-0073, and the collections of information in 21 CFR parts 801 and 809 have been approved under OMB control number 0910-0485.

#### X. Codification of Orders

Under section 513(f)(3) of the FD&C Act, FDA may issue final orders to reclassify devices. FDA will continue to codify classifications and reclassifications in the Code of Federal Regulations (CFR). Changes resulting from final orders will appear in the CFR as newly codified orders. Therefore, under section 513(f)(3), in the proposed order, we are proposing to codify CMV transplant assays in the new 21 CFR 866.3180 under which CMV transplant assays will be renamed quantitative CMV nucleic acid tests for transplant patient management and would be reclassified from class III into class II.

#### XI. Proposed Effective Date

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

#### XII. References

The following references marked with an asterisk (\*) are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Ljungman P., M. Boeckh, H. H. Hirsch, et al., "Definitions of CMV Infection and Disease in Transplant Patients for Use in Clinical Trials." *Clinical Infectious Diseases*, 64(1):87-91, 2017.

2. Singh, N. and A. P. Limaye, "Infections in Solid-Organ Transplant Recipients." *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th Edition. Philadelphia (PA): Elsevier. p. 3440-3452, 2015.

\*3. "Deciding When to Submit a 510(k) for a Change to an Existing Device--Guidance for Industry and Food and Drug Administration Staff," issued October 25, 2017 (available at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM514771>).

\*4. Transcript of the FDA Microbiology Devices Panel Meeting, November 9, 2016 (available at <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/UCM531275.pdf>).

5. Kotton, C. N., D. Kumar, A. M. Caliendo, et. al., "Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation." *Transplantation*, 96(4): 333-360, 2013.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

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

PART 866--IMMUNOLOGY AND MICROBIOLOGY DEVICES

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

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

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

§ 866.3180 Quantitative cytomegalovirus (CMV) nucleic acid tests for transplant patient management.

(a) *Identification.* A quantitative cytomegalovirus (CMV) nucleic acid test for transplant patient management is identified as a device intended for prescription use in the detection of CMV and as an aid in the management of transplant patients to measure CMV deoxyribonucleic acid (DNA) levels in human plasma and/or whole blood 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 developing CMV infection. The test results are intended to be interpreted by qualified healthcare professionals in conjunction with other relevant clinical and laboratory findings.

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

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

(i) A prominent statement that the device is not intended for use as a donor screening test for the presence of CMV DNA in blood or blood products.

(ii) Limitations, which must be updated to reflect current clinical practice. The limitations must include, but are not limited to, statements that indicate:

(A) Test results are to be interpreted by qualified licensed healthcare professionals in conjunction with clinical signs and symptoms and other relevant laboratory results;

(B) Negative test results do not preclude CMV infection or tissue invasive CMV disease, and that CMV test results must not be the sole basis for patient management decisions.

(iii) A detailed explanation of the interpretation of results and acceptance criteria must be provided and include specific warnings regarding the potential for variability in CMV viral load measurement when samples are measured by different devices. Warnings must include the following statement, where applicable: "Due to the potential for variability in CMV viral load measurements across different CMV assays, it is recommended that the same device be used for the quantitation of CMV viral load when managing CMV infection in individual patients."

(iv) A detailed explanation of the principles of operation and procedures for assay performance.

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

(i) Detailed documentation of the device description, including all parts that make up the device, reagents required for use with the CMV assay but not provided, an explanation of the methodology, design of the primer/probe sequences, rationale for the selected gene target, and specifications for amplicon size, guanine-cytosine content, and degree of nucleic acid sequence conservation. The design and nature of all primary, secondary, and tertiary quantitation standards used for calibration must also be described.

(ii) A detailed description of the impact of any software, including software applications and hardware-based devices that incorporate software, on the device's function.

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

(iv) Stability data for reagents provided with the device and indicated specimen types, in addition to the basis for the stability acceptance criteria at all time points chosen across the

spectrum of the device's indicated life cycle, which must include a time point at the end of shelf life.

(v) All stability protocols, including acceptance criteria.

(vi) Final lot release criteria, along with documentation of an appropriate justification that lots released at the extremes of the specifications will meet the claimed analytical and clinical performance characteristics as well as the stability claims.

(vii) Risk analysis and documentation demonstrating how risk control measures are implemented to address device system hazards, such as Failure Modes Effects Analysis and/or Hazard Analysis. This documentation must include a detailed description of a protocol (including all procedures and methods) for the continuous monitoring, identification, and handling of genetic mutations and/or novel CMV strains (e.g., regular review of published literature and annual in silico analysis of target sequences to detect possible primer or probe mismatches). All results of this protocol, including any findings, must be documented.

(viii) Analytical performance testing that includes:

(A) Detailed documentation of the following analytical performance studies: limit of detection, upper and lower limits of quantitation, inclusivity, precision, reproducibility, interference, cross reactivity, carryover, quality control, specimen stability studies, and additional studies as applicable to specimen type and intended use for the device.

(B) Identification of the CMV strains selected for use in analytical studies, which must be representative of clinically relevant circulating strains.

(C) Inclusivity study results obtained with a variety of CMV genotypes as applicable to the specific assay target and supplemented by in silico analysis.

(D) Reproducibility studies that include the testing of three independent production lots.

(E) Documentation of calibration to a standardized reference material that FDA has determined is appropriate for the quantification of CMV DNA (e.g., a recognized consensus standard).

(F) Documentation of traceability performed each time a new lot of the standardized reference material to which the device is traceable is released, or when the field transitions to a new standardized reference material.

(ix) Clinical performance testing that includes:

(A) Detailed documentation of device performance data from either a method comparison study with a comparator that FDA has determined is appropriate, or results from a prospective clinical study demonstrating clinical validity of the device.

(B) Data from patient samples, with an acceptable number of the CMV positive samples containing an analyte concentration near the lower limit of quantitation and any clinically relevant decision points.

(C) The method comparison study must include predefined maximum acceptable differences between the test and comparator method across all primary outcome measures in the clinical study protocol.

(D) The final release test results for each lot used in the clinical study.

Dated: September 15, 2020.

Lauren K. Roth,

Associate Commissioner for Policy.

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