



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2020-N-1088]

Microbiology Devices; Reclassification of Nucleic Acid-Based Hepatitis C Virus Ribonucleic Acid Assay Devices, To Be Renamed Nucleic Acid-Based Hepatitis C Virus Ribonucleic Acid Tests

AGENCY: Food and Drug Administration, HHS.

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

SUMMARY: The Food and Drug Administration (FDA or Agency) is proposing to reclassify nucleic acid-based hepatitis C virus (HCV) ribonucleic acid (RNA) devices intended for the qualitative or quantitative detection or genotyping of HCV RNA, postamendments class III devices (product codes MZP and OBF), into class II (general controls and special controls), subject to premarket notification. FDA is also proposing a new device classification regulation with the name “nucleic acid-based Hepatitis C virus (HCV) ribonucleic acid tests” along with the special controls that the Agency believes are necessary to provide a reasonable assurance of safety and effectiveness for these devices. 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 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 XI 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 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.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking 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-2020-N-1088 for “Reclassification of Nucleic Acid-Based Hepatitis C Virus Ribonucleic Acid Assay Devices, To Be Renamed Nucleic Acid-Based Hepatitis C Virus Ribonucleic Tests.” 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.

- 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 docket, 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.

FOR FURTHER INFORMATION CONTACT: Silke Schlottmann, Division of Microbiology Devices, 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 FD&C Act, as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (Pub. L. 101-629), Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107-250), the Medical Devices Technical Corrections Act (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144), among other amendments, 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 categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (general controls and special controls), and class III (general controls and premarket approval).

Section 513(a)(1) of the FD&C Act defines the three classes of devices. Class I devices are those devices for which the general controls of the FD&C Act (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 (21 U.S.C. 351, 352, 360, 360f, 360h, 360i, or 360j) or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness; or those devices for which insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or to establish special controls to provide such assurance, but because the devices are 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 do not present a potential

unreasonable risk of illness or injury, are to be regulated by general controls (section 513(a)(1)(A) of the FD&C Act). Class II devices are those devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, and for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions the Agency deems necessary to provide such assurance (section 513(a)(1)(B) of the FD&C Act). Class III devices are those devices for which insufficient information exists to determine that general controls and special controls would provide a reasonable assurance of safety and effectiveness, and are 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 present a potential unreasonable risk of illness or injury (section 513(a)(1)(C) of the FD&C Act).

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 and part 807 (21 CFR part 807), subpart E, of the 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) 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 (see section 520(c) of the FD&C Act). Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA (see section 520(c) of the FD&C Act).

In accordance with section 513(f)(3) of the FD&C Act, the Agency is issuing this proposed order to reclassify nucleic acid-based HCV RNA devices intended for the qualitative or quantitative detection or genotyping of HCV RNA, postamendment class III devices, into class II (general controls and special controls), subject to premarket notification because the Agency 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.¹

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

¹ 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 provide reasonable assurance of the safety and effectiveness of the device. FDA has determined that premarket notification is necessary to reasonably assure the safety and effectiveness nucleic acid-based HCV RNA devices intended for the qualitative or quantitative detection or genotyping of HCV RNA. Therefore, the Agency does not intend to exempt these proposed class II devices from premarket notification requirements. If this proposed order is finalized, persons who intend to market this type of device must submit to FDA a premarket notification under section 510(k) of the FD&C Act prior to marketing the device.

II. Regulatory History of the Devices

This proposed order applies to nucleic acid-based HCV RNA devices intended for the qualitative or quantitative detection or genotyping of HCV RNA. These are prescription devices assigned product codes MZP (for qualitative and quantitative HCV RNA tests) and OBF (for HCV RNA genotyping tests) and are collectively referred to as “nucleic acid-based HCV RNA tests.” On July 3, 2001, FDA approved its first nucleic acid-based qualitative HCV RNA test for use as a prescription device as an aid in the diagnosis of active HCV infection in HCV antibody positive individuals (Roche Molecular Systems, Inc.’s COBAS AMPLICOR Hepatitis C Virus (HCV) Test, version 2.0) through its PMA process under section 515 of the FD&C Act (21 U.S.C. 360e). In a July 17, 2002, *Federal Register* notice (67 FR 46990), FDA announced the PMA approval order and the availability of the Summary of Safety and Effectiveness Data (SSED) for this device. Since the first approval order, FDA has approved two additional original PMAs for nucleic-acid based qualitative HCV RNA tests that are prescription devices intended for use as an aid in the diagnosis of active HCV infection in HCV antibody positive individuals

by a qualified licensed healthcare professional in conjunction with other relevant clinical and laboratory findings (hereafter referred to as “qualitative HCV RNA tests”).

On March 28, 2003, FDA approved its first quantitative nucleic acid-based HCV RNA test for use as a prescription device in the management of chronic HCV-infected patients undergoing antiviral therapy (Bayer Healthcare, LLC’s Bayer VERSANT HCV RNA 3.0 Assay (bDNA)) through its PMA process under section 515 of the FD&C Act. In a March 10, 2005, *Federal Register* notice (70 FR 11986), FDA announced the PMA approval order and the availability of the SSED for this device. Since the first approval order, FDA has approved four additional original PMAs for quantitative nucleic acid-based HCV RNA tests that are prescription devices intended for management of chronic HCV-infected patients undergoing antiviral therapy by a qualified licensed healthcare professional in conjunction with other relevant clinical and laboratory findings (hereafter referred to as “quantitative HCV RNA tests”). Three of these tests are approved for both the qualitative detection of HCV RNA as an aid in the diagnosis of active HCV infection and for the quantitation of HCV RNA in the management of chronic HCV-infected patients undergoing antiviral therapy.

On June 20, 2013, CDRH approved its first nucleic acid-based HCV genotyping test for use as a prescription device in the qualitative identification of certain HCV genotypes (Abbott Molecular Inc.’s Abbott RealTime HCV Genotype II) through its PMA process under section 515 of the FD&C Act. In an August 19, 2013, *Federal Register* notice (78 FR 50422), FDA announced the approval order and the availability of the SSED for this device. Since the first approval order, FDA has approved one additional original PMA for nucleic acid-based HCV genotyping test that is a prescription device intended for the qualitative identification of certain

HCV genotypes by a qualified licensed healthcare professional in conjunction with other relevant clinical and laboratory findings (hereafter referred to as “HCV genotyping tests”).

A review of the medical device reporting databases indicates that there is a low number of reported events for nucleic acid-based HCV RNA tests relative to the number of tests conducted using these devices. As of the date of this proposed order, FDA is aware of three class II recalls for these devices and no class I recalls.² The class II recalls occurred between 2004 and 2011 and were related to: (1) an increased frequency of the interfering background due to the conjugate used for detection, (2) underquantitation of a subset of genotype 4 patient specimens, and (3) a software discrepancy between the onboard reagent stability information and that in the package insert. All recalls have been resolved and no patient harm has been identified. These facts, coupled with the low number of reported events, indicate a good safety record for this device class. These recall events reflect the risks to health identified in section V below, and FDA believes the special controls proposed herein, in addition to general controls, can effectively mitigate the risks identified in these recalls.

III. Device Descriptions

Nucleic acid-based HCV RNA tests are postamendments prescription in vitro diagnostic devices classified into class III under section 513(f)(1) of the FD&C Act. Qualitative and quantitative HCV RNA tests are described in FDA’s SSEDs and product code database (assigned product code MZP) as a hybridization and/or nucleic acid amplification assay for the detection and/or quantification of HCV RNA. HCV RNA, when present in samples, are first amplified by qualitative and quantitative HCV RNA tests and then detected by labeled probes that produce a

² Class II recalls are defined in 21 CFR 7.3(m)(2).

qualitative or quantitative signal indicating either the presence/absence of HCV or the amount of HCV in the sample, respectively.

FDA is proposing to reclassify qualitative HCV tests, which are prescription in vitro diagnostic devices intended to determine the presence of HCV RNA in human serum and/or plasma and are intended for use as an aid in the diagnosis of active HCV infection in patients with serological evidence of HCV infection, or other limited circumstances when active HCV infection of the patient is suspected. FDA is also proposing to reclassify quantitative HCV tests that are prescription in vitro diagnostic devices intended to measure the amount of HCV RNA in human serum and/or plasma and are intended as an aid in the diagnosis of active HCV infection, as an aid in the management of chronic HCV-infected patients undergoing or having completed antiviral therapy, or both. These devices are not intended for screening blood, plasma, cell, or tissue donors.

HCV genotyping tests are described in FDA's SSEDs and the product code database (assigned product code OBF) as an in vitro diagnostic device for qualitative identification of eight clinically relevant HCV RNA genotypes. FDA is proposing to reclassify HCV genotyping tests that are nucleic acid-based in vitro diagnostic tests, which are prescription in vitro diagnostic devices intended to identify HCV genotypes in patients with active HCV infection. The tests are intended to be used as an aid in the management of patients with chronic HCV infection to guide the selection of antiviral treatment.

FDA is proposing to reclassify nucleic acid-based HCV RNA tests from class III (general controls and premarket approval) to class II (general controls and special controls) and to establish a new name for the device type that will be within the classification regulation; i.e., nucleic acid-based HCV RNA tests. FDA believes that this name and proposed identification

language most accurately describes these devices. A nucleic acid-based HCV RNA test is tentatively identified as a device intended for prescription use with human serum or plasma from individuals with evidence of HCV antibodies. The test is intended as an aid in the diagnosis of HCV infection in specified populations, and/or as an aid in the management of HCV-infected patients including guiding the selection of genotype-specific treatment in individuals with chronic HCV infection.

Based upon our review experience and consistent with the FD&C Act and FDA's regulations in 21 CFR 860.134, FDA believes that these devices should be reclassified from class III into class II with special controls 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 nucleic acid-based HCV RNA tests. On March 22, 2018, the Microbiology Devices Panel (Panel) of the Medical Devices Advisory Committee convened to discuss and make recommendations regarding the reclassification of nucleic acid-based HCV RNA tests from class III (general controls and premarket approval) into class II (general controls and special controls) (Ref. 1). Panel members unanimously agreed that special controls, in addition to general controls, are necessary and sufficient to mitigate the risks to the health of patients presented by these devices and to provide reasonable assurance of the safety and effectiveness of these devices (Ref. 2). In addition, Panel members generally agreed with the development of special controls as presented by FDA.

FDA agrees and believes that at this time, sufficient data and information exist such that the risks identified in section V below 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 to 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 part 860, subpart C, FDA is proposing to reclassify postamendments nucleic acid-based HCV RNA tests, to be renamed “nucleic acid-based Hepatitis C virus (HCV) ribonucleic acid (RNA) tests,” from class III into class II. FDA believes that, at this time, there are sufficient data and information available to FDA through FDA’s accumulated experience with these devices from review submissions and from published peer-reviewed 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 V below and provide a reasonable assurance of the 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 nucleic acid-based HCV RNA tests such that patients would benefit from increased access to safe and effective tests.

FDA is proposing to create a classification regulation for nucleic acid-based HCV RNA tests that will be reclassified from class III to class II. Under this proposed order, if finalized, nucleic acid-based HCV RNA tests will be identified as prescription devices. 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 nucleic acid-based HCV RNA tests.

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 these nucleic acid-based HCV RNA tests, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the 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 for these types of devices but can instead submit a 510(k) to the Agency for review prior to marketing their device. A 510(k) typically results in a shorter premarket review timeline compared to a PMA, which ultimately provides more timely access of these types of devices to patients.

In addition, the Agency believes that certain changes could be made to nucleic acid-based HCV RNA tests that could significantly affect the safety and effectiveness of those devices and for which a new 510(k) is likely required.³ 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

³ See 21 CFR 807.81(a)(3)(i).

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

It is estimated by the Centers for Disease Control and Prevention that chronic HCV infection in the United States affects at least between 2.7 and 3.9 million people (Ref. 4). HCV infection can be asymptomatic, and accordingly, many HCV-infected individuals are unaware of their HCV infection. Between 20 percent and 30 percent of patients with acute infection, defined as the first 6 months after infection, clear the virus spontaneously while the other 70 percent to 80 percent of individuals become chronically infected with HCV (Ref. 5). Later diagnosis can lead to a more severe disease outcome, and premature death among those who are chronically infected (Ref. 6). Patients who are tested and become aware that they are HCV infected may modify risk behaviors to prevent transmission to others and can be referred for treatment.

If left untreated, patients with chronic HCV infection have a significant risk of developing severe liver disease and/or hepatocellular cancer. Treatment of chronic HCV is highly effective, resulting in a sustained virological response (SVR) considered synonymous with cure. SVR is associated with improved clinical outcome, and a decrease in HCV-associated mortality (Ref. 7). Therefore, diagnosis of HCV infection through devices such as nucleic acid-based HCV RNA tests is essential to ensure that patients are linked to the appropriate care (Ref. 6).

After consideration of FDA's accumulated experience with these devices from review of previous submissions, recommendations of the Panel for the classification of these devices (Ref.

2), and published literature, FDA has identified the following probable risks to health associated with nucleic acid-based HCV RNA tests:

- *Inaccurate interpretation of test results.* Inaccurate interpretation of results by clinicians may negatively influence patient management decisions. Such decisions may include the administration of unnecessary treatment and potential adverse effects, the withholding of treatment, or the choice of an inappropriate treatment, and could lead to adverse effects on patient health such as progressive liver disease, cirrhosis and/or hepatocellular cancer, all of which are known to contribute to patient morbidity and mortality (Ref. 6). Patients with active HCV infection also risk spreading the virus to others
- *Failure of the device to perform as indicated (e.g., inaccurately low or high results, false negative, false positive test results, and inaccurate genotyping results).* Inaccurately low results, false negative results, or inaccurate test results from nucleic acid-based HCV RNA genotyping tests (i.e., the test result is for a genotype that is not the one that the patient is actually infected with) due to failure of the device to perform as indicated may negatively influence patient management decisions. Such decisions may include the withholding of treatment or the choice of an inappropriate treatment, and could lead to adverse effects on patient health such as progressive liver disease, cirrhosis and/or hepatocellular cancer, all of which are known to contribute to patient morbidity and mortality (Ref. 6). Patients with active HCV infection also risk spreading the virus to others. Inaccurately high or false positive test results due to failure of the device to perform may contribute to the unnecessary initiation of treatment. In addition, these results may contribute to potential adverse effects from HCV antiviral drug therapy in the following groups: (1) successfully treated patients who are incorrectly considered

treatment failures, (2) in patients who have spontaneously cleared HCV, or (3) in patients previously treated but suspected of reinfection.

- *Decreased test sensitivity and/or an increased rate of false negative test reporting.* This may occur with patient samples that contain different genotypes, rare de novo mutations in genomic regions of HCV targeted by the device, or that are taken during the time that the patient transitions from acute to chronic infection, which is when HCV viral load can transiently decrease and/or become undetectable in samples before the virus enters into chronic replication.

VI. Summary of the Reasons for Reclassification

FDA believes that nucleic acid-based HCV RNA tests 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 V 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, nucleic acid-based HCV RNA tests can provide significant benefits to clinicians and patients.

FDA's reasons for reclassification are based on the substantial scientific and medical information available regarding the nature, complexity, and risks associated with nucleic acid-based HCV RNA tests in the identified intended use populations (Ref. 1). The safety and

effectiveness of this device type has become well established since the initial approval of the first qualitative HCV RNA test in 2001 (for the detection of HCV RNA in anti-HCV positive individuals), of the first quantitative HCV RNA test in 2003 (for quantitation of HCV RNA in anti-HCV positive individuals), and of the first HCV genotyping test in 2013 (for genotyping of HCV RNA).

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 a reasonable assurance of the safety and effectiveness of nucleic acid-based HCV RNA tests. Table 1 demonstrates how these proposed special controls will mitigate each of the identified risks to health in section V.

The risk of inaccurate interpretation of test results can be mitigated by special controls requiring certain labeling, including providing clearly stated warnings and limitations, device description information, and detailed instructions in the device labeling regarding the interpretation of test results and principles of operation and procedure in performing the test. In addition, when intended for Point of Care use, special controls requiring clinical testing performed in appropriate settings and additional labeling to provide a brief summary of the instructions for use can also mitigate the risk of inaccurate interpretation of test results.

Risks associated with the failure of the device to perform as indicated (e.g., inaccurately low or high results, false negative, false positive test results, and inaccurate genotyping results) can be mitigated through a combination of special controls related to certain labeling requirements, design verification and validation activities, and performance studies. Examples of verification and validation information to be included in the design of the device includes

documentation of a complete device description, calibrators, critical reagents, traceability, and lot release criteria. In addition, design verification and validation must include documentation of performance specifications including analytical and clinical performance criteria. Required statements in labeling can aid in mitigating the occurrence of inaccurate results (for example, a statement that test results are intended to be interpreted by qualified individuals in conjunction with other relevant clinical and laboratory findings). For purposes of clarity, certain proposed special controls apply only to those types of nucleic acid-based HCV tests identified (i.e., HCV RNA tests, qualitative HCV RNA tests, and/or HCV genotyping tests) because, due to differences in the results provided by the different tests, those special controls would not apply to the other types of nucleic acid-based HCV tests. The risks of decreased test sensitivity or an increased rate 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.

Table 1.--Risks to Health and Mitigation Measures for Nucleic Acid-Based HCV RNA Tests

Identified Risks to Health	Mitigation Measures
Inaccurate interpretation of test results	Certain labeling warnings, limitations, results interpretation information, and explanation of procedures.
Failure of the device to perform as indicated	Certain labeling warnings, limitations, results interpretation information, and explanation of procedures in labeling. Certain design verification and validation information including device description, calibrators, critical reagents, traceability, and, lot release criteria. Performance criteria including analytical and clinical performance criteria.
Decreased test sensitivity and/or an increased rate of false negative test reporting	Certain labeling warnings, limitations, results interpretation information, and explanation of procedures in labeling. Certain design verification and validation information including device description, calibrators, critical reagents, traceability, and lot release criteria. Performance criteria including analytical and clinical performance criteria.

If this proposed order is finalized, nucleic acid-based HCV RNA tests will be reclassified into class II (general controls and special controls) and would be subject premarket notification

requirements under section 510(k) of the FD&C Act. As discussed below, the reclassification will be codified in § 866.3170 (21 CFR 866.3170). Firms submitting a premarket notification under section 510(k) of the FD&C Act for nucleic acid-based HCV RNA tests 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 collection 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. This proposed order refers to previously approved FDA collections of information. These collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 820 have been approved under OMB control number 0910-0073; the collections of information in part 807, subpart E, have been approved under OMB control number 0910-0120; 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 nucleic acid-based HCV RNA tests in the new § 866.3170, under which nucleic acid-based HCV RNA tests would be reclassified from class III to 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 at 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 also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. 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. Executive Summary of the FDA Microbiology Devices Panel Meeting, March 22, 2018. Available at <https://www.fda.gov/media/111502/download>.

*2. Transcript of the FDA Microbiology Devices Panel Meeting, March 22, 2018. Available at <https://www.fda.gov/media/119966/download>.

*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/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device>.

*4. Department of Health and Human Services--Viral Hepatitis Action Plan for 2017–2020. Available at <https://www.hhs.gov/sites/default/files/National%20Viral%20Hepatitis%20Action%20Plan%20017-2020.pdf>.

5. Aisyah, D. N., L. Shallcross, A. J. Hully, et. al., “Assessing Hepatitis C Spontaneous Clearance and Understanding Associated Factors--A Systematic Review and Meta-Analysis.” *Journal of Viral Hepatitis*, 25(6): 680-698, 2018.

6. Moorman, A. C., J. Xing, S. Ko, et al., “Late Diagnosis of Hepatitis C Virus Infection in the Chronic Hepatitis Cohort Study (CHeCS): Missed Opportunities for Intervention.” *Hepatology*, 61(5): 1479-1484, 2015.

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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 § 866.3170 to subpart D to read as follows:

§ 866.3170 Nucleic acid-based hepatitis c virus ribonucleic acid tests.

(a) *Identification.* A nucleic acid-based hepatitis C virus (HCV) ribonucleic acid (RNA) test is identified as an in vitro diagnostic device intended for prescription use as an aid in the diagnosis of HCV infection in specified populations, and/or as an aid in the management of HCV-infected patients including guiding the selection of genotype-specific treatment in individuals with chronic HCV infection. The test is intended for use with human serum or plasma from individuals with evidence of HCV antibodies. The test is not intended for use as a donor screening test for the presence of HCV antibodies in blood, blood products, or tissue donors.

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

(1) For all nucleic acid-based HCV RNA tests, the labeling required under 21 CFR 809.10(b) must include:

(i) A prominent statement that the test is not intended for use as a donor screening test for the presence of HCV RNA from human cells, tissues, and cellular and tissue-based products.

(ii) A detailed explanation of the principles of operation and procedures for performing the assay.

(iii) A detailed explanation of the interpretation of results.

(iv) Limitations, which must be updated to reflect current clinical practice and disease presentation and management. These limitations must include, but are not limited to, statements that indicate:

(A) The specimen types for which the device has been cleared and that use of this test kit with specimen types other than those specifically cleared for this device may result in inaccurate test results.

(B) When applicable, that assay performance characteristics have not been established in populations of immunocompromised or immunosuppressed patients or, other populations where test performance may be affected.

(C) Test results are to be interpreted by qualified licensed healthcare professionals in conjunction with the individual's clinical presentation, history, and other laboratory results.

(2) For all nucleic acid-based HCV RNA tests, the design verification and validation must include:

(i) Detailed device description, including the device components, ancillary reagents required but not provided, and an explanation of the device methodology. Additional information appropriate to the technology must be included such as design of primers and probes, rationale for the selected gene targets, specifications for amplicon size, and degree of nucleic acid sequence conservation.

(ii) For devices with assay calibrators, the design and nature of all primary, secondary, and subsequent quantitation standards used for calibration as well as their traceability to a standardized reference material that FDA has determined is appropriate (e.g., a recognized consensus standard). In addition, analytical testing must be performed following the release of a new lot of the standard material that was used for device clearance or approval, or when there is a transition to a new calibration standard.

(iii) Documentation and characterization (e.g., determination of the identity, supplier, purity, and stability) of all critical reagents (including nucleic acid sequences for primers and probes) and protocols for maintaining product integrity.

(iv) Detailed documentation of analytical performance studies conducted as appropriate to the technology, specimen types tested, and intended use of the device, including, but not limited to, limit of detection (LoD), upper and lower limits of quantitation (ULoQ and LLoQ, respectively), linearity, precision, endogenous and exogenous interferences, cross reactivity, carryover, matrix equivalency, and sample and reagent stability. Samples selected for use in analytical studies or used to prepare samples for use in analytical studies must be from subjects with clinically relevant circulating genotypes in the United States. Cross-reactivity studies must include samples from HCV RNA negative subjects with other causes of liver disease, including autoimmune hepatitis, alcoholic liver disease, chronic hepatitis b virus, primary biliary cirrhosis, and nonalcoholic steatohepatitis, when applicable. The effect of each claimed nucleic-acid isolation and purification procedure on detection must be evaluated.

(v) Risk analysis and management strategies, such as Failure Modes Effects Analysis and/or Hazard Analysis and Critical Control Points summaries and their impact on test performance.

(vi) Final release criteria to be used for manufactured test lots with appropriate evidence 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) Multisite reproducibility study that includes the testing of three independent production lots.

(viii) All stability protocols, including acceptance criteria.

(ix) Final release test results for each lot used in clinical studies.

(x) Analytical sensitivity and specificity of the test must be the same or better than that of other cleared or approved tests.

(xi) Lot-to-lot precision studies, as appropriate.

(3) For devices intended for the qualitative detection of HCV RNA, in addition to the special controls listed in paragraphs (b)(1) and (2) of this section, the design verification and validation must include detailed documentation of performance from a multisite clinical study. Performance must be analyzed relative to an FDA cleared or approved qualitative HCV RNA test, or a comparator that FDA has determined is appropriate. This study must be conducted using appropriate patient samples, with appropriate numbers of HCV positive and negative samples in applicable risk categories. Additional genotypes must be validated using appropriate numbers and types of samples. The samples may be a combination of fresh and repository samples, sourced from within and outside the United States, as appropriate. The study designs, including number of samples tested, must be sufficient to meet the following criteria:

(i) Clinical sensitivity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 95 percent.

(ii) Clinical specificity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 96 percent.

(4) For devices intended for the quantitative detection of HCV RNA, the following special controls, in addition to those listed in paragraphs (b)(1) and (2) of this section, apply:

(i) Labeling required under 21 CFR 809.10(b) must include a prominent statement that the test is not intended as a diagnostic test to confirm the presence of active HCV infection, when applicable.

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

(A) Detailed documentation of the following analytical performance studies conducted as appropriate to the technology, specimen types tested, and intended use of the device, including but not limited to: LoD, ULoQ and LLoQ. LoD, LLoQ, and linearity studies must demonstrate acceptable device performance with all HCV genotypes detected by the device.

(B) Detailed documentation of clinical performance testing from either:

(1) A multisite clinical study with an appropriate number of clinical samples from chronically HCV infected patients in which the results are compared to an FDA-cleared or approved quantitative HCV RNA test, or a comparator that FDA has determined is appropriate. This study must include a sufficient number of HCV positive samples containing an analyte concentration near the LLoQ to describe performance at this level. Clinical samples must cover the full range of the device output and must be consistent with the distribution of these genotypes in the U.S. population. Clinical samples may be supplemented with diluted clinical samples for those viral load concentrations that are not sufficiently covered by natural clinical specimens, or

(2) A clinical study with prospectively collected samples demonstrating clinical validity of the device.

(C) Detailed documentation of a qualitative analysis near the lower end of the measuring range demonstrating acceptable performance when used as an aid in diagnosis.

(5) For devices intended for HCV RNA genotyping, in addition to the special controls listed in paragraphs (b)(1) and (2) of this section, design verification and validation must include the following:

(i) Detailed documentation of an analytical performance study demonstrating the LoD for all HCV genotypes detected by the device.

(ii) Detailed documentation, including results, of a multisite clinical study that assesses genotyping accuracy (i.e., the proportion of interpretable results that match with the reference method result) and the genotyping rate (i.e., the proportion of results that were interpretable).

(6) For any nucleic acid-based HCV RNA test intended for Point of Care (PoC) use, the following special controls, in addition to those listed in paragraphs (b)(1) and (2) of this section, apply:

(i) Clinical studies must be conducted at PoC sites.

(ii) Additional labeling must include a brief summary of the instructions for use that are appropriate for use in a PoC environment.

Dated: March 27, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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