FDA Executive Summary

Prepared for the
March 21 - 22, 2018 Meeting on the Reclassification of HIV and HCV Diagnostic Devices
Joint Panel Meeting of the Blood Products Advisory Committee and the Microbiology Devices Panel of the Medical Devices Advisory Committee

Discussion and Recommendations for the Re-Classification of HCV Antibody Tests and Nucleic Acid Based Tests Used as Aids in the Diagnosis of HCV Infection and/or Aids in the Management of Patients Infected with HCV

Silver Spring, Maryland

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The Division of Microbiology Devices (DMD) in the Office of In Vitro Diagnostics and Radiological Health (OIR), in the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA), has regulatory oversight of diagnostic assays for infectious diseases, except for assays for screening tests for blood products and for HIV.

The purpose of the second day of the March 21/22, 2018, CDRH/CBER Advisory Panel Meeting is to discuss the possible reclassification of qualitative Hepatitis C Virus antibody tests for the detection of HCV infection, qualitative and quantitative nucleic acid based HCV tests for the detection and/or quantitation of HCV, and nucleic acid based HCV genotyping tests (hereafter referred to collectively as HCV tests). These tests are currently regulated as Class III, premarket approval (PMA) devices and are under consideration for reclassification into Class II (special controls) for which a premarket notification (510(k)) would be required. FDA is seeking recommendations from panel members and the public on whether sufficient information exists such that the development of special controls (which along with general controls) could mitigate the risks from some or all of these HCV devices such that they would provide a reasonable assurance of safety and effectiveness and therefore, can be eligible for a Class II designation.

In vitro diagnostic devices (IVD(s)) classified into Class III generally have greater FDA oversight and regulatory requirements than Class II devices. During the meeting, the Microbiology Devices (Panel) will be asked to deliberate on the benefits and risks associated with a down classification of the above-mentioned devices to Class II, including a discussion of possible special controls. The Panel will not be asked to formally vote on whether actual reclassification should occur. However, depending on the discussion at this meeting, it may become apparent that reclassification is not appropriate at this time or, alternatively, that special controls can be developed such that would ensure these devices are safe and effective through their Total Product Life Cycle (TPLC) without the oversight required with Class III status and that FDA should pursue the reclassification process.

I. Background

A. Regulation of *In Vitro* Diagnostic Devices

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

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

[1] All citations or references to the Code of Federal Regulations in this document are available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm .

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

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

(1) Class I Devices

Class I devices are primarily devices for which general controls are determined to be sufficient to provide reasonable assurance of device safety and effectiveness. Class I devices may also be devices that do not present a potential unreasonable risk of illness or injury.

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

- Registration of manufacturing facilities and listing of products;
- 510(k) premarket notification requirement;
- Good manufacturing practices (GMPs);
- Quality System procedures that provide for notification of risks and repair, replacement, or refund;
- Other regulatory controls, e.g., labeling, adverse event reporting, misbranding, adulteration of the device.

For example, Respiratory syncytial virus serological reagents are a Class I device as specified in Title 21 of the Code of Federal Regulations (21 CFR 866.3480):

> Sec. 866.3480 Respiratory syncytial virus serological reagents.

[2] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/.

(a) Identification. Respiratory syncytial virus serological reagents are devices that consist of antigens and antisera used in serological tests to identify antibodies to respiratory syncytial virus in serum. Additionally, some of these reagents consist of respiratory syncytial virus antisera conjugated with a fluorescent dye (immunofluorescent reagents) and used to identify respiratory syncytial viruses from clinical specimens or from tissue culture isolates derived from clinical specimens. The identification aids in the diagnosis of respiratory syncytial virus infections and provides epidemiological information on diseases caused by these viruses. Respiratory syncytial viruses cause a number of respiratory tract infections, including the common cold, pharyngitis, and infantile bronchopneumonia.

(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to 866.9.

Due to their low risk, FDA has exempted almost all Class I devices (with the exception of reserved devices)[3] from the requirement for submission of a 510(k) premarket notification requirement (described further below), including devices that were exempted by final regulations published in the Federal Registers of December 7, 1994, and January 16, 1996, and April 13, 2017. If a manufacturer's device falls into a generic category of exempted Class I devices, then a 510(k) submission and FDA clearance are not required before marketing the device in the United States. However, these devices have not been exempted from other general controls as noted above, e.g., registration and listing, GMP regulations, etc.

Further, devices exempt from the premarket notification requirement are only exempt as long as they do not exceed the limitations to their exemptions from the 510(k) requirement. For microbiology devices, the limitations on exemption are found in 21 CFR 866.9. A particularly relevant limitation for many microbiology diagnostic devices is 21 CFR 866.9(c)(6) which provides that a 510(k) must still be submitted if the device is intended "[f]or identifying or inferring the identity of a microorganism directly from clinical material" (21 CFR 866.9(c)(6)), as many microbiology devices are intended to detect and identify the organism directly from clinical specimens. In addition, the limitation on exemption (21 CFR 866.9 (c)(3) is especially relevant for Hepatitis devices "[f]or measuring an analyte that serves as a surrogate marker for screening, diagnosis, or monitoring life-threatening diseases such as acquired immune deficiency syndrome (AIDS), chronic or active hepatitis, tuberculosis, or myocardial infarction or to monitor therapy (21 CFR 866.9(c)(3)). As a consequence of the two aforementioned limitations on exemption, hepatitis *in vitro* diagnostic devices are considered non-exempt devices per section 21 CFR 866.9.

(2) Class II Devices

Class II devices are those that cannot be classified as Class I because general controls alone are insufficient to provide reasonable assurance of device safety and effectiveness, but where there is

[3] For a list of reserved devices see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/3151.cfm

sufficient information to establish special controls that can provide such assurance. Examples of special controls may include:

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

For example, a Cytomegalovirus serological test is a Class II device as specified in Title 21 of the Code of Federal Regulations (21 CFR 866.317:5):

> Sec. 866.3175 Cytomegalovirus serological reagents.
>
> (a) Identification. Cytomegalovirus serological reagents are devices that consist of antigens and antisera used in serological tests to identify antibodies to cytomegalovirus in serum. The identification aids in the diagnosis of diseases caused by cytomegaloviruses (principally cytomegalic inclusion disease) and provides epidemiological information on these diseases. Cytomegalic inclusion disease is a generalized infection of infants and is caused by intrauterine or early postnatal infection with the virus. The disease may cause severe congenital abnormalities, such as microcephaly (abnormal smallness of the head), motor disability, and mental retardation. Cytomegalovirus infection has also been associated with acquired hemolytic anemia, acute and chronic hepatitis, and an infectious mononucleosis-like syndrome.
>
> (b) Classification. Class II (performance standards).

Class I reserved (non-exempt) and Class II submissions are reviewed by FDA under what is referred to as the 510(k) process, named after the section of the statute where the requirement is located. Under the 510(k) paradigm, a device can be cleared for marketing if it is determined to be as safe and effective as a preexisting 'predicate' device (i.e., the device is 'substantially equivalent' to the predicate device).[4] Substantial equivalence broadly encompasses the following:

- The new device has the same intended use as the predicate and the new device has the same technological characteristics as the predicate,

  or

- The new device has the same intended use as the predicate but the new device has different technological characteristics and the information submitted to FDA demonstrates that the device both (a) does not raise new questions of safety and

[4] Devices which are submitted under a 510(k) are 'cleared' for marketing by FDA; under the PMA process (described below) devices are 'approved' by FDA.

effectiveness and (b) is at least as safe and effective as the legally marketed device as demonstrated by the sponsor.

As described on the FDA web site, "a claim of substantial equivalence does not necessarily imply that the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable." The determination of 'substantial equivalence' is therefore a multifaceted examination of the new device focused heavily on the intended use and not independent of the underlying technology.[5]

(3) Class III Devices

Class III devices are those for which insufficient information exists to determine that general and special controls can provide reasonable assurance of the safety and effectiveness, and where these devices are life sustaining or life supporting, of substantial importance in preventing impairment of human health, or present unreasonable risk of illness or injury. Class III devices require 'pre-market approval' (PMA) applications for which additional materials (i.e., information beyond what is required for a class II device) are necessary at the time of regulatory filing by the sponsor/manufacturer. FDA has greater oversight over Class III devices than over Class II and Class I devices.[6]

B. Current Regulation of Qualitative Anti-HCV Tests

FDA regulates qualitative Anti-HCV tests as prescription *in vitro* diagnostic devices intended for use in the detection of antibodies to HCV and as an aid in the presumptive diagnosis of HCV infection in persons with signs and symptoms of hepatitis and in persons at risk for HCV infection. These tests do not determine the state of infection, i.e., active or resolved.

Please refer to Table 2 below for a list of FDA approved Anti-HCV tests. To date, FDA has approved nine PMAs for the detection of Anti-HCV. Anti-HCV tests have an intended use similar to the following:

> The [Anti-HCV assay name] is for the *in vitro* qualitative detection of antibodies to Hepatitis C Virus (HCV) in human adult and pediatric (ages 18 months through 21 years) serum and plasma [Type of Plasma], and/or venous whole blood. Assay results, in conjunction with other laboratory results and clinical information may be used to aid in the presumptive diagnosis of HCV infection in persons with signs and symptoms of

[5] More detailed information regarding premarket applications under the 510(k) process is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm

[6] More detailed information regarding premarket PMA applications is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm

hepatitis and in persons at risk for Hepatitis C infection. The test does not determine the state of infection or associated disease.

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

C. Current Regulation of Nucleic Acid-Based Tests for HCV

(1) Current Regulation of Qualitative HCV RNA Tests

FDA regulates qualitative HCV RNA assays as prescription *in vitro* diagnostic devices intended for the detection of HCV RNA in specimens from individuals with antibody evidence of HCV infection. In these devices, the detection of HCV RNA is evidence of active HCV infection, but does not discriminate between an acute or a chronic HCV infection.

Please refer to Table 3 below for a list of FDA approved qualitative HCV RNA tests. To date, FDA has approved three PMAs for the qualitative detection of HCV RNA. Qualitative HCV RNA tests have an intended use similar to the following:

> The [HCV RNA assay name] is an in vitro diagnostic, nucleic-acid amplification test for the qualitative detection of HCV RNA in human [specimen type]. The [assay name] is indicated for use in the following populations: individuals with antibody evidence of HCV infection with evidence of liver disease, and individuals suspected to be actively infected with HCV with antibody evidence, and individuals at risk for HCV infection with antibodies to HCV. Detection of HCV RNA is evidence of active HCV infection. Detection of HCV RNA does not discriminate between an acute and chronic state of infection or indicate the presence of liver disease.

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

(2) Current Regulation of Quantitative HCV RNA Tests (Viral Load Tests)

FDA regulates quantitative HCV RNA assays as prescription *in vitro* diagnostic devices intended for the quantitation of HCV RNA in specimens from individuals with antibody and HCV RNA evidence of HCV infection.

Please refer to Table 4 below for a list of FDA approved qualitative HCV RNA tests. To date, FDA has approved five PMAs for the quantitative detection of HCV RNA. HCV viral load assays were clinically validated on antibody positive individuals who are known HCV RNA positive and considered for or undergoing HCV antiviral treatment. Quantitative HCV RNA assays have an intended use similar to the following:

> The [HCV RNA assay name] is intended for use as an aid in the management of HCV-infected individuals undergoing anti-viral therapy. The assay measures HCV RNA levels at baseline and during treatment and can be utilized to predict sustained and non-sustained virological response to HCV therapy. The results from the [assay name] must be interpreted within the context of all relevant clinical and laboratory findings.

Recently, FDA has approved nucleic acid based HCV tests that are also intended as an aid in diagnosing HCV infection in antibody positive patients. As such, they were validated for this diagnostic claim with a population of HCV antibody positive individuals with unknown HCV RNA status. These HCV viral load tests provide sensitive qualitative results even when the viral load is below the limit of quantitation. In addition to the above described viral load claim the intended use of these viral load tests include the additional separately validated claim as part of the intended use:

> The [HCV RNA assay name] is intended for use as an aid in the diagnosis of HCV infection in the following populations: individuals with antibody evidence of HCV with evidence of liver disease, individuals suspected to be actively infected with HCV antibody evidence, and individuals at risk for HCV infection with antibodies to HCV. Detection of HCV RNA indicates that the virus is replicating and is therefore evidence of active infection.

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

(3) Current Regulation of HCV Genotyping Tests

FDA regulates HCV genotyping assays as prescription *in vitro* diagnostic devices intended for the qualitative identification of HCV genotypes in specimens from individuals with antibody and HCV RNA evidence of HCV infection.

Currently there are two marketed HCV assays for the qualitative detection of HCV genotypes (please refer to Table 5 for more details on the devices) and each has an intended use similar to the following:

> The [Genotyping assay name] is intended for use as an aid in the management of HCV-infected individuals and in guiding the selection of therapeutic treatment indicated for [specified genotypes] genotypes. The assay is intended for use on patients who are chronically infected with HCV, are being considered for antiviral treatment, and are positive for HCV RNA.

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

II. The Clinical Setting of HCV Infection

A. Public Health Burden

HCV infection represents a significant public health burden. According to the National Notifiable Diseases Surveillance System, the number of new acute HCV infections reported in the U.S. has steadily increased between 2005 and 2015 [1]. Due to underreporting and underrepresentation of certain risk groups, CDC considers the overall number of new infections to be significantly higher than the actual reported number by a factor of 13.9. The true number of new HCV infections may therefore be well above 30,000 cases annually since 2014. Approximately 15% to 25% of acute HCV infected individuals will clear the virus spontaneously, while the other 75% to 85% will develop chronic HCV infection and remain at risk of spreading HCV infection to others if untreated [2]. Based on the 1999 to 2008 National Health and Nutrition Examination Survey, the number of chronically infected HCV patients in the U.S. is estimated at 3.5 million people (between 2.9 to 4.7 million) [3-5]. Chronically infected individuals are at risk for cirrhosis, hepatocellular carcinoma (HCC), other extrahepatic manifestations, liver transplantation, and death, although overall rates of disease progression vary and are significantly impacted by the presence of other comorbidities, such as HIV infection or alcohol use [6, 7]. While the percentage of HCV infected patients who progress to cirrhosis and HCC varies depending on the study, it is estimated that chronic HCV infection progresses to liver cirrhosis in at least 20% of patients within 20 years. These patients are at risk of developing liver failure and/or HCC [8]. Concomitant with the number of HCV-infections, the number of death certificates for which HCV is listed as an underlying or contributing cause of death has steadily increased since 2010 and was estimated to be 19,659 for 2014 [1].

Achieving Sustained Virologic Response (SVR) reduces all-cause mortality and liver-related mortality as well as liver-related morbidity [9-11]. Current guidelines of the *American Association For The Study Of Liver Diseases* and the *Infectious Diseases Society Of America*

(AASLD-IDSA guidelines) state that "the goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response" [12]. The development of highly effective direct acting antivirals (DAAs) as interferon-free treatment regimens has resulted in much higher SVR rates than previously, shorter treatment durations, and fewer adverse effects during treatment. The efficiency and high SVR rates of the new DAA regimens have already been reflected in improved short-term outcomes even though HCV related hepatocellular cancer takes years to develop. Consequently, the impact of new DAA regimens on HCV related mortality may be greater in the future [13-15]. For example, Ioannou et al in a large study from the Veteran Affairs system observed a reduction of HCC risk of up to 71% for cirrhotic and non-cirrhotic patients who achieved SVR [13]. Similarly, Knop and colleagues observed in a prospective study an improvement of liver stiffness (liver stiffness as measured by transient liver elastography is indicative of cirrhosis) between baseline and end of follow up in 88% of patients on DAA regimens [16]. Another prospective study followed 1323 HCV patients with biopsy-proven cirrhosis for five years to assess the impact of SVR on patient outcomes following treatment with DAA regimes. Patients who achieved SVR were found to have a decreased incidence of HCC, liver failure and decreased overall mortality [14]. These results were achieved despite restriction of treatment to patients with progressed liver disease in the first years of DAA availability. States are currently lifting these restrictions. Continued improvements in patient outcomes and reductions in morbidity and mortality may be anticipated, as DAA treatment regimens become more widely available.

B. Testing for HCV

According to the National Viral Hepatitis Action Plan, limited public awareness for viral hepatitis is a persistent challenge, leading to late diagnoses, more severe disease outcomes, transmission through undiagnosed individuals and premature death among those who are chronically infected [17]. HCV infection can be asymptomatic, and accordingly many HCV-infected individuals are unaware of their HCV status and may not undergo HCV testing. Diagnosis of HCV infection is essential to ensure that patients are linked to the appropriate care, to avoid complications associated with chronic HCV and/or to reduce transmission of the virus [18, 19].

(1) Anti-HCV Testing

CDC currently recommends HCV antibody testing for the following individuals:

- Individuals at risk for HCV infection due to contact with contaminated blood or blood products, including current and former injection drug users
- Recipients of clotting factor concentrates made before 1987
- Chronic hemodialysis patients
- Persons with known exposure to HCV such as health care workers following needle sticks involving HCV-positive blood
- Recipients of blood or organs from a donor who tested HCV positive
- Persons with HIV infection

- Children born to HCV-positive mothers
- Adults born during 1945 to 1965

CDC recommended one-time HCV testing of adults born during 1945 to 1965 based on the results of the National Health and Nutrition Examination Survey (NHANES), which is a representative sample of the civilian noninstitutionalized population [20]. The latest AASLD-IDSA guidelines also recommend annual HCV testing for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men [12].

Once a person is tested and found to be HCV antibody positive, they are likely to be antibody positive for life. However, there are certain conditions where HCV antibodies may not be detectable [21]. For example, early acute HCV infection and HCV infection in immunocompromised patients (such as transplant patients on immunosuppressive regimens and HIV patients) can be associated with a false negative anti-HCV result.

Antibody tests only provide evidence of past or current infection. Additional tests, such as HCV nucleic acid assays, are needed to differentiate between active and resolved HCV infection. Subsequent HCV nucleic acid assays in association with HCV genotyping and other clinical characteristics are then used to guide the therapeutic decision making for the management of chronic HCV infection.

Anti-HCV tests have been held to high performance standards because of their role as an initial diagnostic test for HCV infection. In the FDA approved labeling for Anti-HCV devices results of the test were compared to a patient infected status (PIS) as presented in the clinical study. The PIS is defined by the result of an FDA approved Anti-HCV test in combination with the result of an FDA approved HCV RNA test as shown in Table1.

Table 1: Patient Infected Status (PIS) for Anti-HCV Tests

Anti-HCV[a]	**RNA Test**	**PIS Result**[b]	**Interpretation**[c]
Non-Reactive	N/A	Negative	- If patient has no known risk, then no further testing. - If patient has risk, retest in 6 months. - If patient has symptoms but no known risk, retest in 6 months.
Reactive	Non-Reactive	Positive	Resolved
Reactive	Reactive	Positive	Active HCV infection

[a] It is recommended that the FDA approved Anti-HCV test not produce 'equivocal' as the final result.
[b] The results of the investigational Anti-HCV test were compared to the PIS Result
[c] The Interpretation is based on the CDC algorithm (https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_flow.pdf) and the table found at the following link: https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf

Table 2 below summarizes the performance of FDA approved Anti-HCV tests, as presented in the FDA approved labeling (tests are listed in order of approval date). Performance is shown as positive percent agreement (PPA) and negative percent agreement (NPA) when compared to the

PIS[7]. The clinical studies were performed with cohorts that included both symptomatic and asymptomatic patient populations with risk factors for HCV infection. As outlined in Table 2, all HCV antibody tests have a PPA of greater than 99%.

[7]PPA and NPA are used as performance metrics since the comparator in the clinical study is not a recognized gold standard; the terms "sensitivity" and "specificity" are used only when performance of the candidate assay is established in comparison to a recognized gold standard.

Table 2: FDA Approved Anti-HCV Tests in the US

Manuf.	Device*	PMA Number	Date of Approval	PPA [95% CI]	NPA [95% CI]
Roche Diagnostics	Elecsys Anti-HCV II[b]	P140021	6/11/2015	99.6% (558/560) [98.7%-99.96%]	98.8% (1663/1683) [98.2%-99.3%]
OraSure Technologies	OraQuick HCV Rapid Antibody Test[c]	P080027	6/25/2010	99.5%[d] (435/437) [98.4%-99.9%]	99.0%[d] (762/770) [98.0%-99.6%]
				97.9%[e] (708/723) [96.9%-98.8%]	98.5%[e] (923/937) [97.5%-99.2%]
Roche[a] Diagnostics	Elecsys Anti-HCV[b]	P090009	4/29/2010	99.6% (463/465) [98.5%-99.5%]	96.9% (1581/1632) [95.9%-97.7%]
Roche[a] Diagnostics	Elecsys Anti-HCV[b]	P090008	4/29/2010	99.6% (462/464) [98.5%-99.95%]	97.1% (1583/1630) [96.2%-97.9%]
Roche[a] Diagnostics	Elecsys Anti-HCV[b]	P090007	4/29/2010	99.4% (461/464) [98.1%-99.9%]	97.2% (1587/1632) [96.3%-98.0%]
Abbott Laboratories	ARCHITECT Anti-HCV[b]	P050042	6/7/2006	99.53% (214/215) [97.4%-99.99%]	97.6% (1069/1095) [96.5%-99.8%]
Siemens Healthcare	ADVIA Centaur HCV[b]	P030056	12/22/2004	99.9% (1071/1072) [99.5%-100%]	97.5% (1081/1109) [96.4%-98.3%]
Abbott Laboratories	AxSYM Anti-HCV[f]	P970027	2/5/2004	N/A[g]	N/A[g]
Ortho-Clinical Diagnostics	VITROS Anti-HCV[b]	P010021	8/30/2001	99.5% (654/657) [98.7%-99.9%]	98.2% (1930/1965) [97.5%-98.8%]

[*] Device name is hyperlinked to the FDA Summary of Safety and Effectiveness Data.

[a] The Elecsys Anti-HCV assay was approved on three different instruments in three separate PMAs, each with a full set of analytical and clinical studies.

[b] The results are for plasma samples. The other claimed matrices were tested as part of a matrix equivalency study.

[c] The test is approved for fingerstick and venous whole blood.

[d] Results are shown for venous whole blood.

[e] Results are shown for fingerstick whole blood.

[f] The test is no longer marketed (PMA withdrawn).

[g] The individual population results could not be pooled as different methods were used to determine the PIS.

(2) Nucleic Acid-Based Testing for HCV RNA

Nucleic acid based tests for the detection of HCV RNA are typically performed on specimens from Anti-HCV positive patients to determine whether the patient has active or resolved HCV infection. In the future, nucleic acid tests will likely also be used for diagnosis of re-infection in previously treated patients. A positive HCV RNA result in an anti-HCV antibody positive patient

is considered an active HCV infection. However, a HCV RNA test result cannot distinguish between acute or chronic infection. A positive HCV RNA test, in conjunction with an initially positive HCV antibody test, is indicative of chronic HCV infection when the suspected exposure occurred more than 6 months prior to the testing. The patient should be assessed for exposure risks, time of exposure and signs and symptoms of liver disease to arrive at an appropriate diagnosis of chronic HCV infection. Specific situations, such as a person being recently exposed to HCV (e.g., accidental needle stick exposure of healthcare professionals) or having continuous risk of exposure (e.g., through needle/syringe sharing by IV drug users) may merit re-testing for HCV RNA [22].

Table 3 lists FDA approved tests for the detection of HCV RNA in order of approval date. Following the discovery of HCV, HCV diagnostic devices have rapidly changed. When the first qualitative HCV RNA tests were developed, there were no other established HCV RNA tests available to test for the actual presence of HCV RNA in the test specimen. Clinical performance for these early qualitative HCV RNA tests was therefore established by comparing the HCV RNA test result to the clinical diagnosis of hepatitis such that diagnostic tests for liver enzymes, HCV antibodies and liver histology were used to characterize the specimens/patients in the study. After HCV RNA tests became more widely available other qualitative HCV RNA tests were approved based on a comparator that included the actual detection of HCV RNA with a previously approved comparator test. Due to these different comparators, clinical performance cannot be directly compared across the qualitative HCV RNA tests. Table 3 below shows the approved HCV RNA tests and presents their Limit of Detection (LoD) as an important analytical performance parameter.

Table 3: FDA Approved HCV RNA Tests for the Detection of HCV RNA in HCV Antibody Positive Individuals (Qualitative HCV RNA Tests)

Manufacturer	Device*	PMA Number	Approval Date	LoD^{a}_{serum} (IU/mL)	LoD^{a}_{plasma} (IU/mL)
GEN-PROBE	VERSANT TM HCV RNA Qualitative Assay	P020011	11/07/02	0.9 $\log_{10}$ IU/mL (7.5 IU/mL)	N/A
Roche Molecular	AMPLICOR HCV Test, v2.0[b]	P000010	7/05/01	2.0 $\log_{10}$ IU/mL (100 IU/mL)	1.7 $\log_{10}$ IU/mL (50 IU/mL)
Roche Molecular	COBAS AMPLICOR HCV Test, v2.0[b]	P000012	7/03/01	2.0 $\log_{10}$ IU/mL (100 IU/mL)	1.8 $\log_{10}$ IU/mL (60 IU/mL)

* Device name is hyperlinked to the FDA Summary of Safety and Effectiveness Data.

[a] LoD as assessed with the WHO international standard for HCV RNA (Genotype 1a); LoDs can vary for other genotypes.

[b] AMPLICOR HCV and COBAS AMPLICOR HCV have the same chemistry but the AMPLICOR HCV has a manual test procedure and the cobas AMPLICOR HCV has an automated test procedure. Both PMA products no longer marketed and were withdrawn.

Following identification of active infection with a qualitative HCV RNA test, nucleic acid based tests for the quantitation of HCV viral load are used in the management of chronically HCV infected patients. HCV viral load tests are used during treatment to measure HCV RNA levels at baseline, during treatment (e.g., at week 4), at the end of treatment, and at the end of treatment follow-up (i.e., 12 or 24 weeks after the end of treatment) to determine presence or absence of a sustained virological response (SVR). In the past, viral load tests were only validated for their utility in the management of chronic HCV infected individuals, including their ability to predict SVR.

Initial treatment regimens for chronic HCV infection consisted of interferon (subsequently pegylated IFN) and Ribavirin. In 2011, the first generation of NS3/NS4a protease inhibitors (either boceprevir or telaprevir) were FDA-approved for treatment with IFN. In 2013, anti-HCV therapy consisted of a 24 or 48-week treatment course. Treatment success was measured as SVR, defined as an HCV RNA level usually below 25 IU/mL at 24 weeks after the completion of treatment. Viral load measurements were recommended at weeks 4 and 12 on treatment to assess rapid virological response (RVR) and early virological response (EVR). RVR and EVR were predictive for the likelihood of achieving SVR and were consequently used to decide if treatment should be continued (commonly referred to as response guided therapy). Clinical studies of the HCV viral load assays listed in Table 4 demonstrated the ability of the viral load assay to predict SVR to anti-HCV therapy at certain timepoints on treatment.

In 2013, following the approval of Sofosbuvir and subsequent DAA, IFN-based regimens are no longer used as standard of care; DAA-based interferon-free anti-HCV regimens have significantly shorter treatment courses (i.e., 8 to 24 weeks) depending on the regimen, the patient's viral genotype, previous treatment history and cirrhosis status. The new DAA based treatment regimens achieve rapid virologic suppression within the first two to four weeks of treatment. In the majority of patients, viral load is below both the limit of quantitation and the limit of detection at week 4, especially if patients are treatment naïve or non-cirrhotic (e.g., [12, 23, 24]). Even patients with measurable viral loads at week 4 may continue to achieve SVR (e.g., [25, 26], Appendix of [27]). Due to the effectiveness of the new DAA treatment regimens, response guided therapy is no longer necessary for the new DAAs and guidelines discourage modifying antiviral treatment courses based on HCV viral load testing.

The current algorithm for HCV RNA testing still specifies a two-step process: An initial qualitative HCV RNA test is performed and if positive, the patient is then followed by a quantitative HCV RNA test to determine the patient's HCV viral load. This two-step process was necessary because the qualitative HCV RNA assays (approved in 2001 and 2002) were more sensitive than the first approved quantitative HCV viral load test (approved in 2003). Viral load tests approved after 2003 have high sensitivity (low LoD) although some of them have not been validated for their diagnostic capabilities, i.e., for use with HCV antibody positive individuals with unknown RNA status. To establish the performance of the diagnostic capability of the recently approved quantitative HCV RNA assays, clinical samples were compared to a patient infected status (PIS), which was defined as a positive anti-HCV antibody test result plus the RNA test result. Consequently, the diagnostic clinical performance of these assays in Table 4 is presented as PPA and NPA compared with the PIS. These new generation viral load tests are indicated for both the qualitative detection and the quantitation of HCV RNA in specimens from

HCV antibody positive individuals, thereby reducing two-step RNA testing for HCV (with a qualitative RNA test and a viral load test) to a single test.

All viral load tests produce results in which the samples are determined to be one of the following: HCV not detected, HCV detected but not quantifiable, or HCV detected with a specific viral load in IU/mL or detected above the upper limit of quantitation. Table 4 shows the LoD of FDA approved quantitative viral load assays as well as clinical performance (i.e., Positive Percent Agreement [PPA] and Negative Percent Agreement [NPA][8]) in order of approval.

Table 4: FDA Approved HCV RNA Tests for the Quantitation of HCV in Anti-HCV Positive Individuals

Manufacturer	Device*	PMA Number	Approv. Date	LoD[a] serum (IU/mL)	LoD[a] plasma (IU/mL)	PPA[b] (95% CI)	NPA[b] (95% CI)
Hologic, Inc.	Aptima HCV Quant Dx Assay	P160023	2/13/17	0.53 $\log_{10}$ IU/mL 3.4 IU/mL	0.59 $\log_{10}$ IU/mL 3.9 IU/mL	98.8% (96.7-99.6)	100% (95.4-100)
Roche Molecular	cobas-HCV	P150015	10/14/15	1.14 $\log_{10}$ IU/mL 13.7 IU/mL	1.08 $\log_{10}$ IU/mL 12.0 IU/mL	100.0% (97.5-100)	98.8 %[c] (93.3-99.8)
Abbott Molecular Inc.	Abbott RealTime HCV	P100017	5/17/2011	1.08 $\log_{10}$ IU/mL (12 IU/mL)	1.08 $\log_{10}$ IU/mL (12 IU/mL)	N/A	N/A
Roche Molecular	COBAS AmpliPrep/COBAS TaqMan HCV Test	P060030	10/30/2008 02/18/2016[d]	1.26 $\log_{10}$ IU/mL (18 IU/mL)	1.26 $\log_{10}$ IU/mL (18 IU/mL)	100.0% (97.3-100)	100.0% (95.5-100)
Bayer Health Care LLC	Bayer VERSANT HCV RNA 3.0 Assay (bDNA)[e]	P020022	3/28/2003	3.0 $\log_{10}$ IU/mL (1,000 IU/mL)	3.0 $\log_{10}$ IU/mL (1,000 IU/mL)	N/A	N/A

* Device name is hyperlinked to the FDA Summary of Safety and Effectiveness Data.
[a] LoD as assessed with the WHO international standard for HCV RNA (Genotype 1a); LoDs can vary for other HCV genotypes.
[b] PPA and NPA calculated in comparison to Patient Infected Status represent performance of the assay with respect to detecting HCV RNA in antibody positive individuals.
[c] The cobas HCV was approved for use with both, the cobas 6800 and the cobas 8800 with slightly different NPA; the NPA listed here was obtained with the cobas HCV run on the cobas 6800; NPA of the test when run on the cobas 8800 was 100.0% (95% CI: 95.5 - 100.0)
[d] P060030 was originally approved on 10/30/2008 for the quantitation of HCV RNA in patients undergoing anti-HCV treatment; the diagnostic claim was validated and submitted to FDA as a PMA supplement and was approved on 02/18/2016.
[e] PMA product is no longer marketed and was withdrawn

[8] PPA and NPA are used as performance metrics since the comparator in the clinical study is not a recognized gold standard; the terms "sensitivity" and "specificity" are used only when performance of the candidate assay is established in comparison to a recognized gold standard.

AASLD-IDSA recommends testing the HCV genotype of infected patients to guide selection of the most appropriate antiviral regimen and treatment duration as this may be particularly important in the context of previous treatment failure and/or existing resistance associated mutations. Table 5 lists the currently approved HCV Genotyping tests in the order of approval.

Table 5: FDA Approved HCV Genotyping Tests Currently Marketed in the US

Manufacturer	Device*	PMA Number	Date of Approval	Range of Genotyping Accuracy
Siemens Healthcare Diagnostics	VERSANT HCV Genotype 2.0 Assay (LiPA)	P160016	3/14/2017	98.6 to 100%[a]
Abbott Molecular Inc.	Abbott RealTime HCV Genotype II	P120012	6/20/2013	98.7 to 100%[b]

[*] Device name is hyperlinked to the FDA Summary of Safety and Effectiveness Data
[a] Accuracy differs by genotype.
[b].Accuracy differs by genotype. Genotype 6 is not detected by this device

III. Risks to Health

For HCV infection, the risks to health identified by FDA are potential increases in morbidity and mortality for the infected patients, as well as a potential increase in dissemination of infection from untreated individuals. After consideration of the recommendations of professional organizations, other government organizations, FDA's accumulated experience from PMA applications, and the published literature, FDA has identified the following specific risks associated with IVD devices for HCV.

A. Qualitative HCV Antibody Tests

- *A false negative test result* may result in non-diagnosis or a delay in diagnosis of HCV infection, with an associated delay in therapy and potentially increased risk of HCV-related morbidity or mortality. Patients with active infection may unknowingly continue to infect others. False negative results can also lead to unnecessary diagnostic evaluation if alternative etiologies of hepatitis are pursued. False negative tests may occur if the level of antibody in a specimen is below the limit of detection of the assay.

- *A false positive test result* may contribute to unnecessary additional testing and may impact the psychological well-being of the patient. Factors that may increase the rate of false positive test reporting include cross-reactivity with antibodies against other microorganisms or other disease conditions.

B. Qualitative HCV RNA Tests

- *A false negative result* can lead to a misdiagnosis of an actively infected patient as one that has a cleared, or resolved, HCV infection. A false negative test result may therefore delay or prevent a patient from being identified as actively infected and linked to the

appropriate care. The patient could then unknowingly infect others. A delayed or falsely negative result also places the patient at risk for disease associated morbidity or mortality.

In the context of a symptomatic patient, misdiagnosis can also lead to unnecessary testing in pursuit of another potential cause of hepatitis. This may lead to a delay in, or failure to perform, appropriate additional diagnostic procedures (e.g., assessing the severity of HCV-associated liver disease).

Factors that may increase the rate of false negative test reporting include 1) the inability of the test to detect low levels of HCV RNA in patient samples (i.e., tests with a high limit of detection would increase the rate of false negative results), 2) the test's inability to detect RNA from patients infected with different HCV genotypes, 3) microbial interference and 4) endogenous interferents.

- *A false positive result* could lead to a misdiagnosis of active HCV infection. This misdiagnosis can lead to unnecessary diagnostic procedures (e.g., viral load testing, HCV genotyping and additional diagnostic procedures) or psychological trauma to the patient who is concerned about a chronic infection and possible disease consequences.

C. Quantitative HCV RNA Tests (Viral Load Tests)

- *A false negative result* can lead to incorrectly determining SVR after antiviral treatment of an actively infected patient. A false negative test result may therefore lead to withholding or delay of additional anti-HCV treatment and consequently lead to the patient's disease progression. Additionally, the patient can spread their HCV infection to others and increase the burden of HCV infection in the United States.

  Factors that may increase the rate of false negative test reporting include the inability of the test to detect low levels of HCV RNA (i.e., tests with a high limit of detection would increase the false negative rate) and the inability to detect RNA from different HCV genotypes (inclusivity for all genotypes).

- *A false positive result* from a viral load assay could misidentify a patient as a non-responder/relapser (i.e., consider them as an anti-HCV treatment failure) or, if the assay also has a diagnostic claim, could lead to a misdiagnosis of active HCV infection. In both instances, the false positive result can lead to unnecessary treatment and/or psychological trauma to the patient (e.g., concern about a chronic infection that can have severe disease consequences). Unnecessary treatment exposes the patient to potential adverse effects of antiviral treatments. Additionally, misdiagnosis can lead to unnecessary diagnostic procedures (e.g., HCV genotyping).

D. HCV Genotyping Tests

- Although pan-genotype HCV treatment has recently been FDA approved, many current DAA treatment regimens are genotype specific; treatment duration may also be genotype specific. Failure to detect the correct genotype, particularly in the presence of cirrhosis, can result in a suboptimal or incorrect choice of anti-HCV regimen or treatment duration,

increase the risk of treatment failure, expose the patient to the potential adverse effects of HCV antiviral medications, and increase the risk of drug resistance.

Factors that contribute to the failure of a test to detect the correct genotype are genotype inclusivity and cross-reactivity between genotypes.

IV. Proposed Special Controls

FDA considers that the special controls proposed below, in addition to general controls, can mitigate the risks to health for each of the device types as indicated.

The risks associated with HCV tests, as described above, are primarily false positive and false negative results. False results may occur in association with limitations of the device design, such as genotype inclusivity, interference, cross reactivity, analytical sensitivity (i.e., LoD and Lower Limit of Quantitation) and specificity. False positive results may occur in association with microbial interference, cross reactivity and endogenous interference. Some of these risks can be mitigated through the development of special controls, such as specific performance validation studies, labeling mitigations, and inclusion of certain device specific information in the design controls (e.g., design related information).

Currently, HCV diagnostic devices have robust analytical performance (i.e., the devices have a low LoD) and high PPA/NPA point estimates in clinical trials, i.e., equal to or above 98% depending on the specific assay. FDA's primary concern regarding HCV diagnostic devices is maintaining this high performance across different HCV device types over time. Accordingly, performance standards for these devices are proposed in the Special Controls described below. These performance standards would need to be met by original as well as by modified devices.

The special controls listed in the sections below are examples of special controls that could be considered for the HCV tests discussed in this document. The majority of these Special Controls apply to all HCV device types discussed in this document (i.e., Section A below), others are specific for antibody tests, qualitative NAT tests, viral load tests or genotyping tests, respectively (i.e., sections b, c and d below).

Note that, while some of the examples below are special controls for devices of similar technology and/or that present similar risks to health, any panel recommendations should not rely on the assumption that any or all of these special controls will be included in any potential reclassification.

The following are possible special controls that FDA is considering in any reclassification of HCV tests:

A. All HCV Tests

1. A detailed explanation of the interpretation of results must be provided in the device's 21 CFR 809.10(b) compliant labeling, including specific reference to the FDA acceptable

algorithm and information for testing for persons who might have been exposed to HCV within the past 6 months when testing for HCV RNA or follow up testing for HCV antibody is recommended. HCV antibody reactive results are considered presumptive for HCV infection.

2. The device's 809.10 compliant labeling must include the following warning statement "This test is only intended to be used with [insert specimen types]. Other specimen types have not been validated for use with this device."

3. A detailed explanation of the principles of operation and procedures for assay performance must be included in the device's 21 CFR 809.10(b) compliant labeling.

4. The compliant design controls must include the following:

    i. Detailed device description documentation, including the device components, ancillary reagents required but not provided, an explanation of the methodology, and as appropriate for the device type, both antigen(s) and capture antibody design, design of the primer/probe sequences, rationale for the selected gene target, specifications for amplicon size, and degree of nucleic acid sequence conservation.

    ii. For devices with assay calibrators: the documentation must also include the design and nature of all primary, secondary and subsequent quantitation standards used for calibration.

    iii. Detailed documentation for device software, including, but not limited to, software applications and hardware-based devices that incorporate software.

    iv. Calibration standards used in manufacturing this device must be deemed appropriate by FDA. Further, as part of verification and validation activities performed under design controls, analytical testing must be performed following the release of a standard reference lot of the calibration material used for device clearance, or when there is a transition to a new calibration standard.

    v. A list of all critical reagents, including amino acid sequences for antigens, description of antibodies and their epitopes, nucleic acid sequences for primers and probes, and procedures used to ensure that critical reagents are acceptable.

    vi. Detailed documentation of validation processes to support changes to existing manufacturing sites, or the addition of manufacturing sites.

    vii. A design verification summary to establish that design outputs meet design inputs.

    viii. Failure Modes Effects Analysis (FMEA) and/or Hazard Analysis and Critical Control Points (HACCP).

    ix. Final release criteria to be used for manufactured device lots with 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.

x. Stability studies must include an assessment of stability for reagents provided with the device and indicated specimen types and must use acceptance criteria that ensure that analytical and clinical performance characteristics are met when stability is assigned based on the extremes of the acceptance range.

xi. Final release test results for each lot used in clinical study.

xii. Multisite reproducibility study that includes the testing of three independent production lots.

xiii. Robust procedure(s) for addressing complaints, recalls, and an adequate mitigation (e.g., real-time stability program) to the risk of false results due to potential modifications to the device.

5. The 21 CFR 809.10 compliant labeling must include statements, as applicable, indicating that:

   i. The assay performance characteristics have not been established in populations of immunocompromised or immunosuppressed patients or, [other populations where test performance may be affected].

   ii. The device is not intended for use as a donor screening test for the presence of HCV antibodies in blood, blood products and tissue donors.

B. Qualitative HCV Antibody Tests

In addition to the special controls above, that apply to all device types discussed in this document, this section describes possible special controls that would be specific for HCV qualitative antibody tests.

1. Limitations of the device's 809.10 compliant labeling for HCV antibody tests must include the following, where applicable:

   i. "A non-reactive test result does not exclude the possibility of exposure to HCV."
   ii. "The detection of anti-HCV antibodies does not differentiate between acute, chronic, or resolved infection."
   iii. "False negative results may occur due to antibody levels below the detection limit of the assay or if the patient's antibodies do not react with the antigens used in this test."
   iv. For visually read lateral or flow through Anti-HCV devices: "The intensity of the test line does not necessarily correlate with the HCV antibody titer in the specimen."

2. The compliant design controls must include:

   i. Detailed documentation of the following analytical performance studies:

Limit of blank, limit of detection, cutoff determination, precision, reproducibility, drug interference, endogenous interference, cross reactivity, carry-over, seroconversion sensitivity panel testing, genotype detection panel testing, quality control, matrix equivalency (if applicable), sample stability studies, reagent stability studies, and additional studies as applicable to specimen type and intended use for the device. Anti-HCV samples selected for use in analytical studies or used to prepare samples for use in the analytical studies must be from patients with clinically relevant circulating genotype(s) in the United States.

ii. Detailed documentation from a multisite study in which the results from clinical samples that cover the full range of the device output are analyzed relative to a comparator that FDA has determined is acceptable. This study must be conducted using patient samples consisting of HCV positive and negative samples. HCV antibody tests must meet the following minimum performance:

- Positive Percent Agreement: Point estimate must be at least 99% with a lower limit of the two-sided 95% CI of at least 95%.
- Negative Percent Agreement: Point estimate must be at least 97% with a lower limit of the two-sided 95% CI of at least 96%

C. Qualitative HCV RNA Tests

1. The device's 21 CFR 809.10 compliant labeling must include the following statements where applicable to the specific device:

   i. "Negative test results do not preclude active HCV infection, and test results should not be the sole basis for patient management decisions."

   ii. "Mutations within the highly conserved regions of a viral genome covered by the test may affect its primer and/or probe binding resulting in the failure to detect the presence of virus."

   iii. "The magnitude of the test result is not indicative of the concentration of HCV RNA or virus particles in the specimen".

   iv. "This test is not intended to be used to monitor individuals who are undergoing treatment."

2. The compliant design controls for qualitative HCV RNA tests must include:

   i. Detailed documentation of the following analytical performance studies: limit of detection (LoD), precision, reproducibility, interference, cross reactivity, carry-over, and cross contamination, specimen stability, quality control and additional studies as applicable to the technology, the specimen type and/or the intended use for the device. The LoD study must demonstrate acceptable detection of and acceptable performance with all HCV genotypes as applicable to the specific assay target. Documentation must include calibration to a reference standard that FDA has determined is acceptable for the detection of HCV RNA.

ii. Detailed documentation from a multisite clinical study with study subjects who have previously obtained a positive anti-HCV result. The study must include anti-HCV negative subjects with known non-hepatitis related liver diseases (e.g., autoimmune hepatitis, alcoholic liver disease, chronic HBV, primary biliary cirrhosis, NASH and/or fatty liver disease). The results of the candidate device must be compared to a FDA acceptable nucleic acid based HCV test. Qualitative HCV tests must be demonstrated to meet the following performance:

(A) Sensitivity: Point estimate must be at least 99% with a lower limit of the two-sided 95% CI of at least 95%.

(B) Specificity: Point estimate must be at least 98.5 with a lower limit of the two-sided 95% CI of at least 95%.

D. Quantitative HCV RNA Tests (Viral Load Tests)

1. For nucleic-acid based IVDs that are solely for the quantitation of HCV RNA in persons with detectable anti-HCV antibody, the device's 21 CFR 809.10 compliant labeling must include the following statements, where applicable:

   i. "This test is not intended as a diagnostic test to confirm the presence of active HCV infection."

   ii. Negative test results do not preclude active HCV infection, and test results should not be the sole basis for patient management decisions".

   iii. "Mutations within the highly conserved regions of a viral genome covered by the test may affect its primer and/or probe binding resulting in the under-quantitation of virus or failure to detect the presence of virus."

2. The compliant design controls for HCV viral load tests must include:

   i. Detailed documentation of the following analytical performance studies: limit of detection, linearity, upper and lower limits of quantitation (ULoQ, LLoQ, respectively), inclusivity, precision, reproducibility, interference, cross reactivity, carry-over, and cross contamination, specimen stability, quality control and additional studies as applicable to the technology, the specimen type and/or the intended use for the device. LoD, LLoQ and linearity studies must demonstrate acceptable device performance with all HCV genotypes as applicable to the specific assay target. In addition, the LoD must be consistent with applicable guidelines for the treatment of HCV and determining sustained virological response (SVR). Documentation must include calibration to a reference standard that FDA has determined is acceptable for the detection and/or quantitation of HCV RNA.

   Detailed documentation from a multisite clinical study with clinical samples from chronically HCV infected patients with detectable and undetectable viral loads to a comparator that FDA has determined is acceptable. Clinical samples should cover the

full range of the device output but may be supplemented with diluted clinical samples for those viral load concentrations that are not sufficiently covered by natural clinical specimens. This study must be conducted using patient samples, with an acceptable number of the HCV positive samples containing an analyte concentration near the lower limit of quantitation. The three most prevalent HCV genotypes in the U.S. should be included in the study population and the distribution of the genotypes should be reflective of the distribution of these genotypes in the U.S. population. HCV viral load tests must demonstrated to meet the following performance:

(A) Sensitivity: Point estimate must be at least 99% with a lower limit of the two-sided 95% CI of at least 95%.

(B) Specificity: Point estimate must be at least 98.5% with a lower limit of the two-sided 95% CI of at least 95%.

E. HCV Genotyping Tests

1. The compliant design controls for HCV genotyping tests must include:

   i. Detailed documentation of the following analytical performance studies: limit of detection (LoD), precision, reproducibility, accuracy across the expected measuring range, detection of mixed infections, interference, cross reactivity, carry-over, and cross contamination, specimen stability, quality control and additional studies as applicable to the technology, the specimen type and/or the intended use for the device. The LoD study must demonstrate acceptable detection of all diagnostically relevant HCV genotypes, including subtypes 1a and 1b, as applicable to the specific assay target. Documentation must include calibration to a reference standard that FDA has determined is acceptable for the detection of HCV RNA.

   ii. Detailed documentation of a multisite clinical study that compares results from an FDA acceptable number of anti-HCV and HCV RNA positive clinical samples that cover all diagnostically relevant genotypes detected by the device to a comparator that FDA has determined is acceptable. This study must be conducted using patient samples, with an acceptable number of the HCV positive samples for each genotype containing analyte concentrations near the lower limit of detection. The following parameters must be assessed and must be demonstrated to meet the performance as indicated:

      - Genotyping rate is the proportion of valid genotype results that were interpretable. Point estimate for the genotyping rate must be at least $\geq 90\%$.

      - Genotyping accuracy is the proportion of interpretable results that match with the reference method results. Point estimate for the genotyping accuracy must be at least $\geq 99\%$.

6. Questions

The reclassification of a device from Class III to Class II is dependent on the extent to which special controls, along with the applicable general controls, are sufficient to provide reasonable assurance of safe and effective use of the diagnostic device. As part of the reclassification process, FDA will publish a proposed order with special controls as part of the new regulation that FDA considers necessary to provide reasonable assurance of safety and effectiveness of the device. In this context, the Panel is asked to please discuss the following:

a. Do Panel members believe that the special controls as described above, in addition to general controls, are sufficient to mitigate the risks to health presented by (1) Anti-HCV tests, (2) Quantitative and Qualitative HCV RNA tests, and/or (3) HCV Genotyping tests?

b. Please include deliberations of the minimum device performance standards (e.g., sensitivity and specificity) proposed above.

7. Appendix I: Definition of HCV Infection

a. Hepatitis C, Acute (2016 Case Definition)

The Definition of acute Hepatitis C can be found under the following link on the CDC webpage: https://wwwn.cdc.gov/nndss/conditions/hepatitis-c-acute/case-definition/2016/

Clinical Criteria:
An illness with discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), AND
(a) jaundice, OR
(b) a peak elevated serum alanine aminotransferase (ALT) level >200 IU/L during the period of acute illness.

Laboratory Criteria for Diagnosis:
A positive test for antibodies to hepatitis C virus (anti-HCV)

Hepatitis C virus detection test:
Nucleic acid test (NAT) for HCV RNA positive (including qualitative, quantitative or genotype testing)

b. Hepatitis C, Chronic (2016 Case Definition)

The Definition of acute Hepatitis C can be found under the following link on the CDC webpage: https://wwwn.cdc.gov/nndss/conditions/hepatitis-c-chronic/case-definition/2016/

Clinical Criteria
No available evidence of clinical and relevant laboratory information indicative of acute infection (refer to the criteria for classification Table VII-B in CSTE position statement 15-ID-03). Most hepatitis C virus (HCV)-infected persons are asymptomatic; however, many have chronic liver disease, which can range from mild to severe.

Laboratory Criteria for Diagnosis

- A positive test for antibodies to hepatitis C virus (anti-HCV)
- Hepatitis C virus detection test: Nucleic acid test (NAT) for HCV RNA positive (including qualitative, quantitative or genotype testing)

8. Appendix II: Recalls & Medical Device Reports (MDRs)

a. Recalls

Table 6 below lists all recalls obtained for HCV in vitro diagnostics over the past 10 years. For HCV Antibody tests, two recalls occurred in the past ten years and only one was directly related to a malfunction of the anti-HCV test device (i.e., other recall was related to the instrument/accessory). For HCV RNA tests, there were only two recalls in the past 10 years, both related to the same device. The most significant recall was related to the under-quantitation of genotype 4 supporting the need for demonstrating genotype inclusivity for HCV diagnostics. HCV genotyping tests have been on the market for a shorter period of time (since June 2013); there were no recalls for genotyping assays as of December 2017.

Table 6: Recalls for HCV In Vitro Diagnostics (Total Product Life Cycle)- HCV Antibody Tests (Product Code MZO)

Trade name	Recall class	Center Classification Date	Firm Name	Recall Reason (Manufacturer)
OraQuick HCV Visual Reference Panel	3	4/18/2016	OraSure Technologies, Inc.	The package insert included with the OraQuick HCV Rapid Antibody test Visual Reference Panel may be incorrect. A customer reported they received the Ora Quick Ebola Visual Reference Panel instead of an OraQuick HCV Visual Reference Panel.
VITROS Immunodiagnostic Products Anti-HCV Reagent Pack	2	9/19/2014	ORTHO-CLINICAL DIAGNOSTICS	VITROS Immunodiagnostic Products Anti-HCV kit lot 9090 has been observed producing sporadic lower than expected VITROS Anti-HCV test results due to an approximate signal loss of up to 66.2% which can result in unexpected negative test results being obtained for reactive sample fluids (quality control and patient samples).
AxSYM Anti-HCV Reagent Pack	2	7/10/2007	Abbott Laboratories	Failure of the AxSYM instrument to open (actuate) some reagent packs from certain lots. The defects can result in probe crashes if not detected prior to placement of the reagent kit on the AxYM instrument.

Table 7: Recalls for HCV In Vitro Diagnostics (Total Product Life Cycle)- HCV RNA Tests (Product Code MZP)

Trade name	Recall class	Center Classification Date	Firm Name	Recall Reason (Manufacturer)
COBAS AmpliPrep / COBAS TaqMan¿ HCV Test, (US-IVD)	2	6/17/2011	Roche Molecular Systems, Inc.	The COBAS Ampliprep/COBAS TaqMan HCV Test has been shown to under-quantitate a subset of genotype 4 patient specimens by approximately 1.0-1.5 log 10 in the absence of any sequence mismatches.
COBAS AMPLICOR HCV Tests Amplilink	2	8/01/2007	Roche Molecular Systems, Inc.	For select COBAS AMPLICOR Tests run on the COBAS AMPLICOR Analyzer in conjunction with AMPLILINK software, a discrepancy has been identified between the onboard working reagent stability information reported by AMPLILINK Software (versions 1.1, 1.3, 1.4 and 2.41) and the stability information provided in the test kit package inserts/method manual.

Table 8: Recalls for HCV In Vitro Diagnostics (Total Product Life Cycle)- HCV Genotyping Tests (Product Code OBF)

Trade name	Recall class	Center Classification Date	Firm Name	Recall Reason (Manufacturer)
N/A	N/A	N/A	N/A	No Recalls as of January 19, 2018

[a] FDA uses the term "recall" when a manufacturer takes a correction or removal action to address a problem with a medical device that violates FDA law. Recalls occur when a medical device is defective, when it could be a risk to health, or when it is both defective and a risk to health. When the FDA learns of a company's correction or removal action, it assesses the health hazard presented by the product and if appropriate assigns to the recall one of the falling classification (I, II, or III) to indicate the relative degree of risk:

Class 1: A situation where there is a reasonable chance that a product will cause serious health problems or death.

Class 2: A situation where a product may cause a temporary or reversible health problem or where there is a slight chance that it will cause serious health problems or death.

Class 3: A situation where a product is not likely to cause any health problem or injury.

b. Medical Device Reports (MDRs):

HCV Antibody Tests

Between 1999 and 2017 there were 193 MDRs for approved HCV antibody tests. The majority of the reports were for false negative (128) and potential false negative (25) results. Only 15 reports were for false positive results (9) and potential false positive results (6). The remaining reports (25) were for other observations, including user errors, instrument errors, control issues. Note, that potential false negative/positive results were defined as those reports that were unable to determine the true test result for the patient or sample due to a lack of patient history, information of previous testing or information on adequate follow up testing. In most instances the occurrence of the reported false negative and potential false negative results was tied to the following circumstances:

- Laboratories performing verification for additional instruments or new reagent lots or
- Testing of samples from patients for whom the clinical history and/or prior positive test results from the same or different device were discordant with the new negative result. Note that a warning is included in all HCV antibody test package inserts pertaining to the interpretation in conjunction with patient's clinical history and adjunctive diagnostic test result.

While some of the devices were more affected than others, FDA does not have evidence that would raise concern about the general performance of approved HCV antibody tests at this time as the numbers are cumulative and may reflect differences in reporting by users and manufacturers and differences in the total number of tests performed.

Note: the number of MDRs in this section was adjusted for incorrect reporting, including: reporting under the wrong product code (13 reports), reporting of devices not approved in the U.S. (such as non U.S. products; 71 reports) and blood screening devices (1 report) for HCV antibodies and multiple reports for the same incident (12 reports).

HCV RNA Tests (qualitative and quantitative):

Between 2006 and 2017 there were 11 MDRs for approved HCV RNA tests. Of those, reporting was done for false positive results (2), incorrect viral loads (7), release of test results from an invalid run (1) and software issue (1). No false negative (0) results related MDRs were submitted. Four (4) of the MDRs were for a HCV viral load test that was discontinued.

Note: the number of MDRs in this section was adjusted for incorrect reporting, including: reporting under the wrong product code (37 reports), reporting of non-approved devices (including CE marked products; 3 reports) and blood screening devices (6 reports) for HCV, reporting of lab accidents independent of the functionality of the HCV device (1 report) and reporting of operator error with an external (non-approved) extraction method (1 report).

HCV Genotyping Tests:

No MDRs for genotyping tests approved in the U.S. since approval of the first genotyping test in 2013.

9. Appendix III: References

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