Update from FDA on Reclassification of HCV and HIV Diagnostic Tests from Class III to Class II

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Disclaimer

My contributions are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.

Proposals

On March 22, 2018, FDA held a Microbiological Devices Advisory Committee meeting to discuss reclassification of HCV diagnostic devices

On July 19, 2018, FDA held a Blood Product Advisory Committee meeting to discuss reclassification of HIV diagnostic devices

Devices affected by the proposal

HCV

- **Anti-HCV (serological) tests**
  8 approved tests
- **Qualitative RNA tests**
  3 approved tests (1 currently marketed)
- **Quantitative (viral load) RNA tests**
  5 approved tests (4 currently marketed)
- **Genotyping tests**
  2 approved tests currently marketed

➢ **NOT considered:** Blood donor screening

HIV

- **Serological diagnostic and supplemental tests**
  8 point of care (CLIA-waived)
  11 lab-based
  6 supplemental
- **NAT diagnostic and supplemental tests**
  1 diagnostic
  1 supplemental

➢ **NOT considered:** Home use, viral load, blood donor screening

How FDA considers device risk and classification

Basis of pre-market device approval: Balance of benefit and risk

- **Safety**

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

- **Effectiveness**

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

Safety/risks to health

- **A false negative test result:**

  May lead to a patient not receiving follow-up testing and linkage to medical care; healthcare providers may pursue other etiologies (e.g., non-viral hepatitis, etc.)

- **A false positive result:**

  May contribute to unnecessary follow-up testing, additional diagnostic testing, and psychological stress to the patient

- **False low or high result:**

  May contribute to changes in patient management

HCV reclassification proposal

Intended Use:
Anti-HCV (serology) tests

"The […] assay is an immunoassay for the *in vitro* qualitative detection of antibodies to hepatitis C virus (HCV) in…serum and plasma. 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 hepatitis and in persons at risk for hepatitis C infection. The test does not determine the state of infection or associated disease."

Proposed special controls: Clinical performance of anti-HCV tests

Clinical performance	Sensitivity/PPA (Lower bound of 95% CI)	Specificity/NPA (Lower bound of 95% CI)
Anti- HCV Test	99% (LB = 95%)	97% (LB = 96%)

Labeling limitations are the same as for the class III device:

- Non-reactive test result does not exclude exposure to HCV
- Detection of HCV antibodies does not differentiate between acute, chronic, or resolved infection
- Lateral Flow tests: Intensity of the test line does not necessarily correlate with the HCV antibody titer in the specimen

Intended Use:
Qualitative HCV RNA tests

"The […] assay is an *in vitro* nucleic acid amplification assay for the detection of hepatitis C virus (HCV) RNA in human plasma or serum.... as an aid in diagnosis of active HCV infection in individuals with antibody evidence of HCV infection.

Detection of HCV RNA does not discriminate between an acute and chronic state of infection or indicate the presence of liver disease."

Intended Use:
Quantitative HCV RNA tests

Diagnostic/Viral Load:

"The […] assay is a test used for both detection and quantitation of Hepatitis C virus (HCV) RNA in fresh and frozen human serum and plasma from HCV-infected individuals.

The […] assay is indicated for use as an aid in the diagnosis of active HCV infection in the following populations... Detection of HCV RNA indicates that the virus is replicating and, therefore, is evidence of active infection. Detection of HCV RNA does not discriminate between acute and chronic states of infection.

The […] assay is also indicated for use as an aid in the management of HCV-infected patients undergoing HCV antiviral drug therapy. The assay can be used to measure HCV RNA levels periodically prior to, during, and after treatment to determine sustained virological response (SVR) or nonsustained virological response."

Genotyping:

"The […] assay is …for *in vitro* diagnostic use, which identifies Hepatitis C virus (HCV) genotypes in human serum or plasma samples.

The […] assay is intended to be used as an aid in the management of patients with chronic HCV infection to guide the selection of antiviral treatment."

Proposed special control: Clinical performance of HCV NAT tests

HCV Test	Sensitivity/PPA (Lower bound of 95% CI)	Specificity/NPA (Lower bound of 95% CI)
Diagnostic RNA Test and Viral Load Tests	99% (LB*: ≥ 95%)	98.5% (LB: ≥ 95%)
	Genotyping Rate**	**Accuracy*****
Genotyping Tests	≥ 90%	≥ 99%

*LB: Lower Bound of the two-sided 95% Confidence Interval

**Genotyping rate: proportion of valid genotype results that were interpretable

*** Genotyping accuracy: proportion of interpretable results that match with the reference method results

Proposed HCV special controls

- Detailed device description that specifies critical components:
  - Antigen(s), antibody[ies], primers, probes, etc.
- Labeling mitigations are the same as for the class III device:
  - Limitations regarding non-reactive results
  - Warnings regarding non-validated populations
  - Warnings regarding non-validated uses
  - Warnings regarding use for blood screening

Proposed HCV special controls

No changes from analytical study design and criteria from class III requirements:

- Traceability:
  5th WHO International Standard for HCV RNA for Nucleic Acid Amplification Technique-Based Assays, 2015; NIBSC code: 14/150 (Human Plasma)
- LoB/LoD
- Cutoff
- Linearity (LLoQ and ULoQ)
- Cross Reactivity
- Interference (endogenous & other liver related conditions)
- Precision/Reproducibility/Accuracy
- Sample Stability
- Reagent Stability

HIV reclassification proposal

Intended uses: HIV tests

Point of care:

"The […] test is intended for use as a point of care test to aid in the diagnosis of infection with HIV. It is not intended for use in screening blood, plasma, cell, or tissue donors."

Lab-based:

"The […] test is intended to be used as an aid in the diagnosis of infection with HIV. It is not intended for use in screening blood or plasma donors, cell, or tissue donors."

Supplemental:

"The […] test is intended for use as an additional, more specific test for [HIV antibodies] in specimens …which are found to be repeatedly reactive by [approved diagnostic test]. It is not intended for screening blood donors."

Proposed special control: Clinical performance of HIV diagnostic tests

HIV Dx Test	**Sensitivity:** Lower bound of 95% CI	**Specificity:** Lower bound of 95% CI
Point of Care	≥ 98%	≥ 98%
Lab-based	≥ 99%	≥ 99%

Proposed HIV special controls

- Analytical study design and performance are the same as for class III tests
- Clinical sample populations are the same as for class III tests
- Submission of manufacturing and QS summaries
- Submission of complaint logs
- Device-type specific labeling requirements

Panel recommendations

- HCV and HIV
  - Unanimous recommendation for reclassification
  - Discussion of sample sizes, performance criteria, CLIA-waived criteria
- Additional comments
  - Recommendation that FDA also consider reclassification of HIV viral load tests

What is the process for writing and publishing proposed orders?

- Proposed order with special controls written by the Division charged with regulating the device with input from other affected Offices, Centers
- Clearance from Division, Office, Center Reg Staff, Center
- Review and clearance from FDA Office of Chief Counsel
- Publication of proposed order in Federal Register

What happens next?

- FDA will publish proposed orders in the Federal Register seeking public comments on each proposal
  - Include proposed special controls
  - FDA will consider and respond to all comments to the proposed order
- FDA will issue a final orders identifying the appropriate class with device-specific regulations
  - If class III, continue to be regulated as PMAs
  - If class II, new devices are submitted as 510(k)s, existing devices are reclassified and released from PMA requirements
  - All devices must follow special controls requirements

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Thank you!

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Link to HCV materials:

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm597841.htm

Link to HIV materials:

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm597841.htm