

Draft Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Hepatitis A Serological Assays for the Clinical Laboratory Diagnosis of Hepatitis A Virus

DRAFT GUIDANCE

**This guidance document is being distributed for comment purposes only.
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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

**Division of Microbiology Devices
Office of *In Vitro* Diagnostic Evaluation and Safety**

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Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This draft guidance document was developed as a special controls guidance document to support the reclassification of hepatitis A virus serological assays [immunoglobulin M (IgM) antibody, immunoglobulin G (IgG) antibody, and total antibodies (IgM and IgG)] into class II. Hepatitis A virus (HAV) serological assays are devices that consist of antigens and antisera for the detection of HAV-specific IgM, IgG, or total antibodies (IgM and IgG), in human serum or plasma. These devices are used for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis or for determining if an individual has been previously infected with HAV. The detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by HAV in conjunction with other clinical laboratory findings. These devices are not intended for screening blood or solid or soft tissue donors.

This draft guidance is issued in conjunction with a *Federal Register* notice announcing the proposal to reclassify HAV serological assays [IgM antibody, IgG antibody and total antibodies (IgM and IgG)] from class III to class II and to codify the classification at 21 CFR

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866.3310.¹ This guidance document is issued for comment purposes only. If a final rule to reclassify this device type is not issued, this guidance document will not be issued as a special control.

Following the effective date of a final rule reclassifying these devices, any firm submitting a premarket notification (510(k)) for an HAV serological assay will need to address the risks covered in the special controls guidance document. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to HAV serological assays and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of HAV serological assays. A manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR part 807, subpart E, (2) address the specific risks to health associated with HAV serological assays identified in this guidance and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This guidance document identifies the classification regulation and product code for HAV serological assays (Refer to Section 4 – **Scope**). In addition, other sections of this guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these assays and lead to a timely 510(k) review and clearance. This

¹ Unlike other classification regulations in 21 CFR part 866, subpart D, which use the term “reagents” in their titles, FDA is using “assays” to refer to this device type because this term more accurately reflects the devices within this type.

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document supplements other FDA documents regarding the specific content of a 510(k) submission. You should also refer to 21 CFR 807.87 and CDRH's **Device Advice** <http://www.fda.gov/cdrh/devadvice/>.

As described in “**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**,” <http://www.fda.gov/cdrh/ode/parad510.html>, a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 10 for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary report

We recommend that the summary report contain:

- A description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and,

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when appropriate, detailed, labeled drawings of the device. Refer to section 6 for specific information that we recommend you include in the device description for devices of the type covered by this guidance document. You should also submit an “indications for use” enclosure.²

- A description of device design requirements.
- An identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device’s design and the results of this analysis. (Refer to Section 5 for the risks to health generally associated with the use of this device that FDA has identified.)
- A discussion of the device characteristics that address the risks identified in this guidance document, as well as any additional risks identified in your risk analysis.
- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 7-9 of this guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.³ (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)
- If you choose to rely on a recognized standard for any part of the device design or testing, you may include either: (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed; or (2) a declaration of conformity to the standard.⁴ Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the Act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA,**

² Refer to <http://www.fda.gov/cdrh/ode/indicate.html>

³ If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

⁴ See Required Elements for a Declaration of Conformity to a Recognized Standard (**Screening Checklist for All Premarket Notification [510(K)] Submissions**), <http://www.fda.gov/cdrh/ode/reqrecstand.html>.

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<http://www.fda.gov/cdrh/ode/guidance/1131.html>.

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a 510(k) submission for HAV serological assays.

4. Scope

The scope of this document is limited to Hepatitis A Virus Serological Assays [IgM antibody, IgG antibody, and total antibodies (IgM and IgG)] (product code: LOL):

In the companion proposed rule, FDA is proposing the following identification:

Hepatitis A virus serological assays are devices that consist of antigens and antisera for the detection of hepatitis A virus-specific IgM, IgG, or total antibodies (IgM and IgG), in human serum or plasma. These devices are used for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis or for determining if an individual has been previously infected with the hepatitis A virus. The detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by hepatitis A virus in conjunction with other clinical laboratory findings. These devices are not intended for screening blood or solid or soft tissue donors.

5. Risks to Health

There are no known *direct* risks to an individual's health associated with the device. However, failure of HAV serological assays to perform as indicated or an error in interpretation of results may lead to improper patient management. There are no clinical features that distinguish HAV infection from infection by other etiologic agents of hepatitis such as hepatitis B virus (HBV) or hepatitis C virus (HCV). HAV serological assays are

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used to aid in this distinction. Therefore, false test results could contribute to improper patient management, which includes misdiagnosis.

A false negative measurement with failure to detect HAV-specific IgM would misdiagnose an active HAV infection. False negative HAV serological assays results may place individuals infected with preexisting liver disease at risk for not receiving appropriate therapy. Such false negative test results may also have serious adverse public health consequences because HAV infected individuals, e.g., food-handlers, may not receive appropriate counseling in regard to prevention of communicating HAV infection to others. It has also been shown that HAV infection in individuals with preexisting liver disease, e.g., HCV infection, has been associated with an increased rate of fulminant hepatitis and mortality [References 1-3]. The administration of HAV-specific hyperimmune globulin may help to prevent or improve the clinical manifestations of disease if given within two weeks of infection as prophylaxis, although it is generally not helpful in the acute phase of HAV infection [Ref. 4]. In healthy individuals, HAV infections are generally self-limiting without serious consequences, with no chronic or persistent hepatitis [Ref. 5].

In addition, the failure to detect HAV-specific total or IgG antibodies would result in misdiagnosis of past infection and may cause individuals to erroneously receive vaccination for HAV. This would be of minimal risk, however, since there is no contraindication for an individual immune to HAV receiving HAV vaccination.

A false positive measurement can result in incorrect diagnosis of active or past HAV infection. If HAV-specific total antibodies are detected erroneously, an individual may not receive the vaccine for HAV and could continue to be at risk for HAV infection. A false positive anti-HAV IgM result also has public health considerations because the majority of state health departments are required to follow-up reported acute HAV infections. This would place an undue burden on state health department resources.

In the table below, FDA has identified the risk to health generally associated with the use of assays for HAV-specific antibodies addressed in this document. The measures recommended to mitigate this identified risk are given in this guidance document, as shown in the table below. We recommend that you conduct a risk analysis, prior to submitting your premarket notification, to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address the risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Improper patient management	Sections 6-10

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6. Device Description

We recommend that you include the following in your device description:

- a description of the method that your device uses to detect HAV-specific IgM, IgG, or total antibodies (e.g., Enzyme Immunoassay)
- a description of the reagent components included with the kit
- information on the antibodies detected or measured
- a clear explanation for the specific controls and calibrators to be used in the assay
- a description of the primary purpose for the quality control material.

In your description of reagent components, you should furnish the antigen source and explain how it was characterized. If a recombinant antigen is used, you should supply specific information concerning the specific HAV epitopes present on the antigen and specific information for antigen characterization. For monoclonal antibodies, you should give specific information concerning HAV epitopes that will be detected, and provide appropriate antibody characterization.

7. Performance Characteristics

General Study Recommendations

We recommend that you test specimens from individuals that have been vaccinated against HAV. You should evaluate a baseline specimen (prevaccination) and a post vaccination specimen collected two to four weeks post vaccination from individuals aged two years and greater. In your study, you should include all vaccines that are currently U.S. licensed. If the assay's capture antigen is different than the vaccine strain, you should explain why this will not produce a false negative result when testing for immunity due to vaccination.

Analytical Studies

Specimen collection and handling conditions

We recommend that you substantiate statements in your labeling about specimen storage and transport by assessing whether the device can maintain acceptable performance (e.g., reproducibility) over the storage times and temperatures recommended to users. For example, an appropriate study may include an analysis of aliquots stored under the conditions of time, temperature, or number of freeze/thaw cycles that you recommend to users of the device. We recommend that you state the criteria for an acceptable range of recoveries under the recommended storage and handling conditions. [See "Procedures for

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Handling and Processing of Blood Specimens;” Approved Guideline, National Committee for Clinical Laboratory Standards (NCCLS), Document H18-A.]

Reproducibility

We recommend that you characterize intra- and inter-assay reproducibility according to guidelines provided in the “User Protocol for Evaluation of Qualitative Test Performance;” Approved Guideline, NCCLS, EP12-A. This document includes guidelines for experimental design, statistical analysis, and a format for stating performance claims. We recommend that you use patient samples, your assay calibrator(s), and the quality control materials that you supply or recommend for your device for this characterization. We recommend that you evaluate reproducibility at relevant measurements, including levels near medical decision points and measurements near the limits of the reportable range.

If your device is indicated for use in matrices other than serum, we recommend that you establish the reproducibility of the assays in each matrix, e.g., EDTA anticoagulated plasma.

We recommend that you include the following items:

- point estimates of the concentration for levels of anti-HAV
- standard deviations of intra- and inter-assay reproducibility
- sites at which the reproducibility protocol was run
- number of days, runs, and observations
- number of sites and/or operators.

We recommend that you identify which factors (e.g., instrument calibration, reagent lots, and operators) were held constant and which were varied during the evaluation. Describe the computational methods, if they are different from that described in the most current NCCLS EP12-A, and “Evaluation of Precision Performance of Clinical Chemistry Devices;” Approved Guideline-2nd Edition, NCCLS Document EP5-A2.

If your assay requires, or you recommend, automated instrumentation, we recommend that you perform the above-mentioned reproducibility with three different instrument builds, i.e., different instrument serial numbers.

Interference

We recommend that you characterize the effects of potential interferents on assay performance. Examples of experimental designs, including guidelines for selecting interferents for testing, are described in detail in “Interference Testing in Clinical Chemistry; Approved Guideline,” NCCLS, EP7-A. Potential sources of interference can include compounds normally found in serum, such as triolein (triglycerides), hemoglobin,

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bilirubin, and serum albumin, as well as potential serum-based interference by rheumatoid factor (RF), anti-nuclear antibodies (ANA), and heterophilic antibodies.

We recommend that you include the following items:

- types and levels of interferents tested
- antibody level in the sample, including description of how the levels of antibodies were determined
- number of replicates tested
- definition or method for computing interference.

We recommend that you identify any observed trends in bias (i.e., negative or positive) and indicate the range of observed recoveries in the presence of the particular interferent. This approach is more informative than listing average recoveries alone. We recommend that you state your criteria or level for determining non-interference.

You may not need to perform additional interference testing with potential interferents of your assay that have already been identified in literature or by other sources. However, you may address additional potential interferents with appropriate citations in the labeling.

Cross-reactivity

We recommend that you include data on assay specificity by measuring the cross-reactivity of your device with antibodies to other relevant microorganisms. In particular, studies should be performed to characterize performance in the presence of antibodies to other viruses that cause hepatitis [e.g., Epstein Barr Virus (EBV), HBV, HCV, cytomegalovirus (CMV), rubeola virus, mumps virus, and varicella zoster virus (VZV)], and other microorganisms that cause hepatitis (e.g., *Toxoplasma gondii*). If your antigen is recombinant, we recommend that you provide cross-reactivity studies against the recombinant vector. For HAV IgM assays, we recommend that you include performance in the presence of such factors as rheumatoid factor, anti-nuclear antibodies, and human anti-mouse antibodies.

Cut-off points

We recommend that you furnish data to explain how your clinically relevant cut-off point was selected and established. You should provide information on the use of an equivocal zone for testing. If you believe an equivocal zone is inappropriate, you should provide an explanation for this since there is not a confirmation assay for anti-HAV.

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Other analytical studies

We recommend that you test seroconversion panels. Many of these panels are commercially available. If a commercial panel is used, we recommend that you reassess the reported reactivity with a legally marketed assay.

We recommend that you test against recognized standards for anti-HAV, e.g., Paul Ehrlich-Institute or World Health Organization (National Institute for Biological Standards and Control) standards, to determine the assay's analytical sensitivity, i.e., limit of detection (LoD).

If a matrix other than serum is recommended, e.g., EDTA or sodium heparin anticoagulated plasma, you should furnish information demonstrating that there is no or minimal assay effect when these anticoagulants are compared to serum.

8. Prevalence (Expected Values)

We recommend that you establish the prevalence of HAV antibodies in a normal population (healthy individuals without symptoms) using the specified cut-off. You should assay a statistically significant number of samples that are representative of the intended use, clinical utility, and matrix of the samples. It is only necessary to furnish results using your device. We recommend that you summarize the distribution of the population according to age groups (in decades), gender, geographical area, and the number of positive, negative, and equivocal results. We recommend that blood donors not be used for this study.

9. Methods Comparison

We recommend that you evaluate your assay at three sites, one of which may be the manufacturer's site. We recommend that you assess performance in the testing environment where the device will ultimately be used (i.e., clinical laboratory) by individuals who will use the test in clinical practice (e.g., trained technologists). We recommend that you initially analyze data from each study site separately to evaluate any inter-site variation and include results of the analysis in the 510(k) summary report. It may be possible to pool clinical study results from the individual sites in the package insert if you can demonstrate that there are no significant differences in the results or populations among sites. Before initiating any clinical study, you may contact the Division of Microbiology Devices.

So that acceptance criteria or data summaries can be best interpreted during the review, we recommend that you provide appropriate specific information concerning protocols. The information is also necessary to aid users in interpreting information in your labeling. For example, when referring to NCCLS protocols or guidelines, we recommend that you indicate which specific aspects of the protocols or guidelines you followed.

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Detectability and Comparative Performance

We recommend that you determine the detectability of antibody to HAV by comparing test performance with a legally marketed device (predicate device) or by testing against an appropriate algorithm that will diagnose HAV acute and past infection. Prospective collection of specimens is recommended. However, repository banks may be used as the source for samples if they contain well characterized specimens that were collected from one site over a contiguous time period. This characterization should include information supporting sample integrity, demonstrating appropriate selection, and clinical laboratory characterization of samples being used from a repository bank. You should consider and address sources of bias.

Sample Selection, Inclusion and Exclusion Criteria

We recommend that you evaluate samples from the intended use population (i.e., individuals with signs and symptoms of hepatitis) in a prospective study, and provide a clear description of how the samples were selected, including reasons that samples were excluded.

Appropriate sample size of the indicated population depends on factors such as reproducibility, interference, and other performance characteristics of the test. We recommend that you provide a statistical justification to support the sample size of the study population.

Presentation of Results

We recommend that you furnish line data for all studies. You may supply this information electronically using Microsoft EXCEL, delimited text files, or SAS files.

10. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in submitting labeling that satisfies the requirements of 21 CFR 807.87(e) and preparing final labeling.⁵

Directions for Use

You should provide clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should

⁵ Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR part 801 and 21 CFR 809.10 before a medical device is introduced into interstate commerce.

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encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

Quality Control

We recommend that you provide a description of quality control recommendations in the labeling and specify what your quality control material will measure.

Precautions for use

We recommend that you address issues concerning safe use of your assay with statements in the labeling, such as the following:

Human samples and blood-derived products may be routinely processed with minimum risk using the procedures described. Human source components of this device were tested and found negative for anti-HIV (types 1 and 2), anti-HCV, and HBsAg by FDA recommended (approved/licensed) tests. Because no test method can offer complete assurance that laboratory specimens do not contain HIV, hepatitis B virus, or other infectious agents, specimens should be handled at the Biosafety Level 2 (BL2) as recommended for any potentially infectious human serum or blood specimen in the CDC-NIH manual, Biosafety in Microbiological and Biomedical Laboratories, 3rd Edition, 1993 and NCCLS Approved Guideline M29-A, Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue.

Precautions for Interpretations

We recommend that you address issues concerning patient safety with statements in the labeling, such as the following:

Assay results should be interpreted only in the context of other clinical laboratory findings and the total clinical status of the individual. It has been shown that a viremic window exists with individuals infected with HAV where the individual may be symptomatic for hepatitis, but anti-HAV IgM nonreactive [Ref. 6].

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