

Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Hepatitis A Virus Serological Assays

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Preface

Public Comment

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Table of Contents

1.	Introduction.....	4
2.	Background.....	5
3.	The Content and Format of an Abbreviated 510(k) Submission.....	6
4.	Scope.....	8
5.	Risks to Health.....	8
6.	Device Description.....	9
7.	Performance Characteristics.....	10
8.	Prevalence (Expected Values).....	12
9.	Methods Comparison.....	13
10.	Labeling.....	14

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Class II Special Controls Guidance Document: Hepatitis A Virus Serological Assays

This guidance represents 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 special controls guidance document was developed to support the reclassification of hepatitis A virus serological assays [that detect immunoglobulin M (IgM), immunoglobulin G (IgG), or 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 to determine if an individual has been previously infected with HAV, or as an aid to identify HAV-susceptible individuals. 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 guidance is issued in conjunction with a *Federal Register* notice announcing the reclassification of HAV serological assays from class III into class II, and codifying the classification at 21 CFR 866.3310.¹

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

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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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

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at <http://www.fda.gov/cdrh/modact/leastburdensome.html>.

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 document, 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 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

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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 development and testing of your device 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 type 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, 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.

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

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(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**, <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 the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

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.

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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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 [that detect IgM, IgG, or total antibodies (IgM and IgG)] (product code: LOL):

In the companion rule FDA has identified these devices, classified under 21 CFR 866.3310, as follows:

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 to determine if an individual has been previously infected with HAV, or as an aid to identify HAV-susceptible individuals. 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 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 could lead to misdiagnosis of an active HAV infection. False negative HAV serological assay results may place individuals infected with preexisting liver disease at risk for not receiving appropriate therapy. Such false negative test results also may have serious adverse public health consequences because HAV infected individuals, e.g., food-handlers, may not receive appropriate counseling regarding how to prevent infecting others with HAV. It has also been shown that HAV infection in individuals with preexisting liver disease, e.g., HCV infection, is 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 2 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].

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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. Hepatitis A virus infection is a public health issue and a reportable disease to the Centers for Disease Control and Prevention. State health laboratories are required to determine whether reported cases of HAV infection are true or false; a false positive anti-HAV IgM result places an undue burden on state health department resources [Ref. 6].

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 7-10

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 provide 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

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give specific information concerning HAV epitopes detected by the assay, 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 (pre-vaccination) and a post-vaccination specimen collected no earlier than 4 weeks post vaccination from individuals aged two years and greater.⁵ 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. If the antigen used in the assay is the same strain, and has been treated in the same manner as the vaccine, the above testing will not be necessary [Ref. 7].

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., assay precision) 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 [Ref. 8].

Precision Testing

You should conduct internal precision testing (i.e., at the manufacturer's site) in accordance with CLSI, EP5-A2 [Ref. 9]. Precision testing performed in accordance with CLSI, EP15-A2 [Ref. 10] should be conducted at three external sites.

We recommend that you characterize samples used for intra- and inter-assay precision testing according to guidelines provided in the CLSI, EP12-A [Ref. 11].

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.

⁵ Due to the HAV vaccine's high efficacy, there is not a recommendation to test post vaccination for vaccine efficacy. Pre-vaccination testing may be desired where anti-HAV prevalence is high and previous vaccination history is unknown. [Hepatitis A, Epidemiology and Prevention of Vaccine-Preventable Diseases, 8th Edition, National Immunization Program, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.] Therefore, anti-HAV IgG and total antibody assays should demonstrate their ability to detect vaccine induced anti-HAV so that previously immunized individuals will not be revaccinated.

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We recommend that you evaluate precision at relevant measurements, including levels near medical decision points and measurements near the limits of the reportable range.

We recommend that you include the following items in your 510(k):

- point estimates of the concentration for levels of anti-HAV
- sites at which the precision protocol was run
- number of days, runs, and observations
- number of sites and/or operators
- standard deviations of intra- and inter-assay precision with exact 95% confidence intervals

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 CLSI EP15-A2 and CLSI EP5-A2.

If your assay requires, or you recommend, automated instrumentation, we recommend that you perform the above-mentioned precision 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 CLSI, EP7-A [Ref. 12]. Potential sources of interference can include compounds normally found in serum, such as triolein (triglycerides), hemoglobin, bilirubin, and serum albumin.

We recommend that you include the following items in your 510(k):

- types and levels of interferents tested
- levels of antibody in the sample, including a description of how the levels 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,

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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, you should perform studies 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 provide 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.

Other analytical studies

We recommend that you test seroconversion panels. The panels should incorporate specimens prior to the appearance of the analyte and, in the case of anti-HAV IgM, when the analyte begins to wane. Many of these panels are commercially available. If you use a commercial panel, we recommend that you reassess its 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 provide information demonstrating that there is minimal (or no) assay effect when these anticoagulants are compared to serum. We recommended that this testing be done in a manner analogous to the evaluation described for method comparison in CLSI, EP9-A2 [Ref. 13] and the World Health Organization's, Use of Anticoagulants in Diagnostic Laboratory Investigations [Ref. 14].

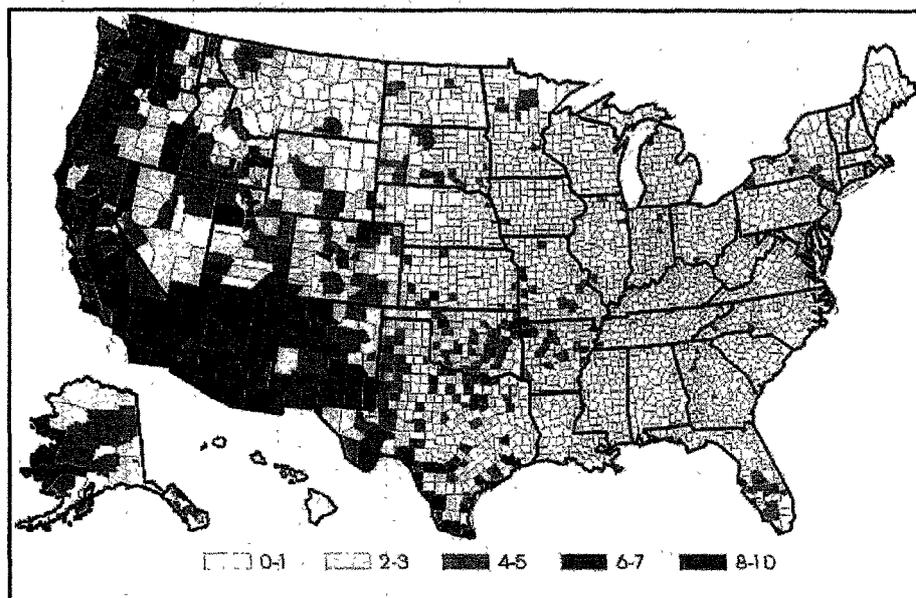
8. Prevalence (Expected Values)

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 test a

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statistically significant number of samples that are consistent with the current U.S. census for age, gender, and ethnicity. Since HAV infection occurs sporadically within the U.S., with more cases being reported from the Western U.S. (Figure 1), we suggest that prevalence studies be conducted in the Eastern U.S. (low prevalence) and the Western U.S (high prevalence). You should provide results based on your device. For Expected Values testing, results based on other devices are not needed. 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.

Number of years that reported incidence of hepatitis A exceeded 10 cases per 100,000*, by county — 1987-1997



*Approximately the national average during 1987-1997.

Figure 1 Source: National Notifiable Diseases Surveillance System. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(No. RR-12):p. 7.

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 consult the Division of Microbiology Devices.

So that we can best interpret acceptance criteria or data summaries during the review, we recommend that you provide appropriate specific information concerning protocols. This

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information is also necessary to aid users in interpreting information in your labeling. For example, when referring to CLSI protocols or guidelines, we recommend that you indicate which specific aspects of the protocols or guidelines you followed.

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. We recommend prospective collection of specimens from individuals with signs and symptoms of acute hepatitis, e.g., hepatology or gastroenterology clinic patients. You may supplement these studies with well-characterized specimens obtained from repository banks. This specimen characterization should include information supporting sample integrity, appropriate selection, and clinical laboratory testing results. You should consider and address sources of bias. Since acute HAV prevalence is relatively low in the U.S., reactive specimens, especially those specimens containing anti-HAV IgM, may be obtained from non-U.S. sources. The information you provide concerning sample characterization of non-U.S. specimens should be the same as that for specimens from the U.S.

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 precision, 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 provide 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). 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.

The following suggestions are aimed at assisting you in submitting labeling that satisfies these requirements and preparing final labeling.

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

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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 CLSI 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. 15].

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