Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: AFP-L3% Immunological Test Systems

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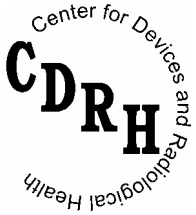
For questions regarding this document, contact Maria Chan at 240-276-0493 or by e-mail at maria.chan@fda.hhs.gov.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Immunology and Hematology Devices

Preface

Public Comment:

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. Please identify your comments with the Docket No. 2005D-0342. Comments may not be acted upon by the Agency until the document is next revised or updated.

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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 guidance document was developed as a special control to support the classification of the AFP-L3% (percent of L3 subfraction of alpha-fetoprotein to total AFP) immunological test systems into class II (special controls). An AFP-L3% immunological test system is an in vitro device that consists of reagents and an automated instrument used to quantitatively measure, by immunochemical techniques, AFP and AFP-L3 subfraction in human serum. The device is intended for in vitro diagnostic use as an aid in the risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma, in conjunction with other laboratory findings, imaging studies, and clinical assessment.

This guidance is issued in conjunction with a *Federal Register* notice announcing the classification of the AFP-L3% immunological test system. Any firm submitting a 510(k) (premarket notification) for an AFP-L3% immunological test system will need to address the issues covered in the special control guidance. 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

The issues identified in this guidance document represent those that we believe need to 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 statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to 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, provide reasonable assurance of the safety and effectiveness of AFP-L3% immunological test systems. A manufacturer who intends to market a device of this 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 807, Subpart E, (2) address the specific risks to health associated with the AFP-L3% immunological test system 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 the AFP-L3% immunological test system (Refer to Section 4 – **Scope**). In addition, other sections of this guidance document list the risk 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 systems and lead to a timely premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87 and other FDA documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, http://www.fda.gov/cdrh/manual/510kprt1.html.

As explained in "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance** ,"[1] a manufacturer may submit either a Traditional 510(k) or an Abbreviated 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly when FDA has issued a guidance document that provides recommendations on what should be addressed in a submission for the device. Alternatively, manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

[1] http://www.fda.gov/cdrh/ode/parad510.html

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 device development and testing and the methods or tests used. The report should also include 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 21 CFR 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 you should include in the labeling for this type of device.)

Summary report

We recommend that the summary report contain the following:

- A description of the device and its intended use. You should also submit an "indications for use" enclosure[2].
- A description of the device design. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device.
- 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.)

[2] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format

- 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 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) present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls under 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 all of 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.

4. Scope

[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.

The scope of this document is limited to the following devices as described in 21 CFR 866.6030 (product code NSF):

21 CFR 866.6030 AFP-L3% Immunological Test System.
An AFP-L3% immunological test system is an in vitro device that consists of reagents and an automated instrument used to quantitatively measure, by immunochemical techniques, AFP and AFP-L3 subfraction in human serum. The device is intended for in vitro diagnostic use as an aid in the risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma in conjunction with other laboratory findings, imaging studies, and clinical assessment.

5. Risks to Health

Failure of the AFP-L3% immunological test system to perform as indicated or error in interpretation of results could lead to inaccurate risk assessment and improper management of patients with chronic liver diseases. Specifically, a falsely low AFP-L3% could result in a determination that the patient is at a lower risk of developing hepatocellular carcinoma, which could delay appropriate monitoring and treatment. A falsely high AFP-L3% could result in a determination that the patient is at a higher risk for hepatocellular carcinoma, which could lead to unnecessary evaluation and testing or inappropriate treatment decisions. Use of assay results without consideration of other laboratory findings, imaging studies, and clinical assessment could also pose a risk.

In the table below, FDA has identified the risks to health generally associated with the use of the AFP-L3% immunological test systems addressed in this document. The measures recommended to mitigate these identified risks 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 a particular 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***
Inaccurate risk assessment and improper patient management due to false positive or false negative results.	Sections 7-10

6. Device Description

In your 510(k), you should identify the regulation, the product code and a legally marketed predicate device. In order to help FDA efficiently review all aspects of your device compared to the predicate, we recommend that you include a table that outlines the similarities and differences between the predicate and your device.

Key issues in the review of a new device are the specific intended use, the type of specimens tested, and the technology utilized. You should include the following descriptive information to adequately characterize the new device.

Intended Use

You should clearly describe the intended use of the device. The intended use should specify the analyte(s) the device is intended to detect, the general clinical utility of detecting the analyte, and the specific population(s) to which the device is targeted.

Some devices may have multiple intended uses. When unique and separate studies are needed to support the multiple intended uses, we recommend that you submit separate applications for each intended use. You should consult the Division of Immunology and Hematology Devices for advice on submitting applications for devices with multiple intended uses.

Device description

You should describe in detail the methodology used by your device. You should also include a description of the reagent components in the kit. Where applicable, you should describe the quality control design specifications in place. Illustrations or photographs of non-standard equipment or methods can be helpful in understanding novel methodologies. You may submit appropriate peer-reviewed literature references relevant to the technology of the device in addition to the descriptive information to adequately describe the new device.

Instrumentation and software

If your device uses specific, dedicated instrumentation (whether manufactured by you, or by another company), you should provide a copy of the manual for the specified instrumentation. You should also include the following information, with results to support your descriptions where appropriate:

- Characterization, including information on how the instrument assigns values or interprets assay variables.
- Calibration, including description of how the instrument is calibrated and the materials used in calibration.
- Uncertainties, including a description of potential sources and estimates of uncertainties in results introduced by hardware components.

If you specify a particular instrument (by manufacturer or brand) you should assure that any changes made to the instrument (by you or the manufacturer) are tracked. If changes

introduce new or different assay performance issues, you should assure proper validation of your device under the changed conditions.

If your system includes software, you should submit software documentation, detailed in accordance with the level of concern (See: "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices; Final*," http://www.fda.gov/cdrh/ode/guidance/337.html. You should determine the Level of Concern prior to the mitigation of hazards. *In vitro* diagnostic devices of this type are considered a moderate level of concern, because software flaws could indirectly affect the patient and potentially result in injury because of the action or inaction of a healthcare provider who does not get accurate information.

You should include the following points, as appropriate, in preparing software documentation for FDA review:

- Full description of the software design. Your software should not include utilities that are specifically designed to support uses beyond those in your intended use. You should also consider privacy and security issues in your design. Information about some of these issues may be found at the following website regarding the Health Insurance Portability and Accountability Act (HIPAA) http://aspe.os.dhhs.gov/admnsimp.

- Hazard analysis based on critical thinking about the device design and the impact of any failure of subsystem components, such as signal detection and analysis, data storage, system communications and cyber-security in relationship to incorrect patient reports, instrument failures, and operator safety.

- Documentation of complete verification and validation (V&V) activities for the version of software that will be submitted to demonstrate substantial equivalence. You should also submit information regarding validation of the compatibility of assay software with any instrumentation software.

- If the information you include in the 510(k) is based on a version other than the release version, you should identify all differences in the 510(k) and detail how these differences (including any unresolved anomalies) impact the safety and effectiveness of the device.

Below are additional references to help you develop and maintain your device under good software life cycle practices consistent with FDA regulations.

- General Principles of Software Validation; Final Guidance for Industry and FDA Staff; available on the FDA Web site at: http://www.fda.gov/cdrh/comp/guidance/938.pdf.
- Guidance for Off-the-Shelf Software Use in Medical Devices; Final; available on the FDA Web site at: http://www.fda.gov/cdrh/ode/guidance/585.pdf.
- 21 CFR 820.30 Subpart C – Design Controls of the Quality System Regulation.

- ISO 14971-1; Medical devices - Risk management - Part 1: Application of risk analysis.
- AAMI SW68:2001; Medical device software - Software life cycle processes.

7. Performance Characteristics

General Study Recommendation

Whenever possible, you should include patient samples derived from the intended use population (i.e., patients with chronic liver disease) in the analytical protocols described below.

You should evaluate your assay in two or more geographically dispersed external sites, in addition to the manufacturer's site. Generally, you should 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). You should initially analyze data separately to evaluate any inter-site variation and include results of the analysis in the 510(k) submission. It may be appropriate to pool results from the individual sites in the package insert if you demonstrate that there are no significant differences in the results among sites. Before initiating your clinical study, you may contact the Division of Immunology and Hematology Devices for input on your protocol.

You should provide specific information concerning protocols so that FDA can interpret acceptance criteria or data summaries during the review. For example, when referring to Clinical Laboratory Standard Institute (CLSI) protocols or guidelines, you should indicate which specific aspects of the protocols or guidelines you followed. We recommend that you include protocol specifics in your labeling, in order to aid users in interpreting information in your labeling.

Performance Characteristics

Precision

You should characterize repeatability (within-run), within-lab precision, and reproducibility across sites, using patient samples or pools. We recommend that you follow guidelines provided in "Evaluation of Precision Performance of Clinical Chemistry Devices" (CLSI document EP5-A). That document includes guidelines for experimental design, computations, and a format for stating performance claims. You should evaluate precision at relevant AFP-L3% measurements, including levels near medical decision points and near the lower limit of the reportable range. We recommend that you include 3 or more sites, multiple lots and multiple instruments in your evaluation.

In the description of your study, you should identify which factors (e.g., instrument calibration, reagent lots, operators) were held constant and which were varied during the evaluation, and describe the computational methods, if they are different from that described in CLSI document EP5-A. You should also include the following information:

- sample types (e.g., matrix, origin, preparation)
- number of days, runs, and observations
- number of sites and/or operators
- target concentrations
- description of the sites at which the precision protocol was run
- observed means and standard deviations

Interference

You should 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" (CLSI document EP7-A). Potential sources of interference can include compounds normally found in whole blood, such as triglycerides, hemoglobin, bilirubin, and albumin; anti-oxidants, such as vitamins C and E; as well as typical drugs used to treat chronic liver disease, such as cirrhosis and viral hepatitis.

Typically, interference studies involve adding the potential interferent to the patient sample and determining any bias in the recovery of AFP-L3% relative to a control sample with no added interferent.

You should describe the following parameters concerning your study design:

- types and levels of interferents tested
- sample types
- concentrations of AFP, AFP-L3 subfraction, and AFP-L3% observed in the presence and absence of the interferent
- your definition or equation for computing interference
- your criteria for interference, e.g., inaccuracies less than X% at interferent levels of Y (concentration)

You should indicate the range of observed recoveries in the presence of the particular interferent. We recommend that you indicate any observed trends in bias (e.g., increases or decreases in observed measures as a function of interferent concentration).

Cross-reactivity

You should evaluate assay specificity by measuring the cross-reactivity of your device with samples derived from patients with other gastrointestinal (GI) cancers and benign disease, such as stomach, pancreatic, and colon cancers and cirrhosis and viral hepatitis. If you are using synthesized or extracted substances to evaluate cross-reactivity, you should evaluate the purity of these substances, and include this information in your 510(k).

Limit of Detection

You should determine the limit of detection of your device. The limit of detection represents the lowest level of AFP-L3% that can be reliably detected by the device and distinguished from zero. You should describe the study design (e.g., samples used, measurements, calculations) you used for making this determination and your results. See "Protocols for Determination of Limits of Detection of Quantitation" (CLSI document EP17-A) for further discussion of determination of limits of detection.

Linearity

You should verify the linear range of your device. We recommend that you follow the guidelines in "Evaluation of the Linearity of Quantitative Analytical Methods," Approved Guideline, CLSI document EP6-A. You should describe your study design (e.g., sample types and preparation, measurements, computational methods), the linear range of the assay, and the acceptance criteria you used to determine this range.

Calibrators and Control Materials

If your device includes calibrators and controls, you should provide the following information in your 510k):

- Protocol and acceptance criteria for real-time or accelerated stability studies for opened and unopened calibrators and controls. This should include the methods or analyses you used and your acceptance criteria for recovery at the expiration date.

- Protocol and acceptance criteria for value assignment and validation of the various calibrator and control levels. This should include the methods or analyses used.

- Identification of traceability to a domestic or international standard reference material, such as the 1st International standard for AFP from NIBSC.

For information about calibrators marketed separately as class II devices under 21 CFR 862.1150, see the guidance "Abbreviated 510(k) Submissions for *In Vitro* Diagnostic Calibrators," http://www.fda.gov/cdrh/ode/calibrator.html.

Specimen collection and handling conditions

You should substantiate the recommendations in your labeling for specimen storage and transport. We recommend that you determine whether the device can maintain acceptable performance (e.g., precision, bias) over the specimen storage times and temperatures (including freeze-thaw cycles) that you recommend in your labeling. You should describe results and the performance criteria you used to determine the storage conditions.

8. Method Comparison

Study Design:

You should compare results obtained with your device to those obtained with a legally marketed predicate device with similar indications for use. We recommend that you also compare to a recognized reference method (if available), especially if there are broad differences in methodology/technology between the new device and the predicate device. We recommend that you follow guidelines provided in "Method Comparison and Bias Estimation Using Patient Samples"; Approved guideline, CLSI document EP9-A.

You should design your study so that the results will demonstrate the association between results of your test and the relative risk profile of the patients represented by the samples, for the development of hepatocellular carcinoma. In particular, results should demonstrate the correlation between the frequency of occurrence of hepatocellular carcinoma and the AFP-L3% results obtained with your test. The study should take into account the time frame for risk assessment that you indicate in your labeling claims. For example, if labeling indicates that the test assesses risk of developing hepatocellular carcinoma within 3 years, the samples you analyze in the study should include longitudinal samples from patients across 3 years. Before initiating this study, you may contact the Division of Immunology and Hematology Devices for input on your proposed study design.

Presentation of Results:

The results you provide should demonstrate the correlation observed between AFP-L3% values and the relative risk profile of studied patients for the development of hepatocellular carcinoma.

You should stratify results according to demographic factors (e.g., age and sex), if these factors have the potential to bias the results.

You should include plots of results from the new assay (y-axis) versus the predicate (x-axis), including all data points, the estimated regression line and the line of identity. Data points should represent individual measurements. You should provide a description of the analytical method used to fit the regression line and results of regression analysis, including the slope and intercept with their 95% confidence limits, the standard error of the estimate (calculated in the y direction), and a correlation coefficient. We recommend that you employ Deming regression, or another method that accounts for variability in both test systems, when appropriate.

9. Expected Values

The L-3 subfraction of AFP is normally not found in normal healthy subjects but is specifically produced when a normal liver cell transforms into a hepatocarcinoma. Therefore, we recommend that your data and labeling demonstrate the absence of AFP-L3% in healthy individuals, benign liver diseases, and other GI cancers and benign diseases. We

recommend that you refer to the document "How to Define and Determine Reference Intervals in the Clinical Laboratory"; Approved Guideline CLSI document C-28.

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 preparing labeling that satisfies these requirements. Although final labeling is not required for 510(k) clearance, final labeling for *in vitro* diagnostic devices must comply with requirements of 21 CFR 809.10 before an *in vitro* diagnostic device is introduced into interstate commerce.

Intended Use

The intended use should be compatible with the performance characteristics of the assay and the patient populations tested in the studies.

Principle of the Method

You should include a clear and concise description of the technological features of the device and how the device is to be used on patients. In addition, the labeling should include a description of the reagent components provided and instrumentation required to run the assay.

Directions for use

You should include clear instructions for the assay procedure.

Specimen collection and handling conditions/stability

You should include the acceptance criteria for specimen stability and integrity parameters. You should also clearly state the validated conditions for specimen transport, storage, temperature, and specified number of freeze/thaw cycles.

Quality Control

You should provide a description of quality control recommendations. This should include a clear explanation of the controls to be used with the assay and the expected results for the control material.

Instrumentation

You should provide a user manual that addresses all components of the specified instrumentation. Your user manual should include an adequate description of the role of the software and the user interface with the software, as well as results of performance testing to demonstrate that the software functions as designed. We recommend that you

include pictorial representations of computer screens, graphical user interfaces (GUIs), and other elements that aid the user in correctly using the software.

The user manual, where possible, should also include descriptions of how the user can recognize incorrect operation or failure of the instrumentation, and a troubleshooting guide.

If general purpose instrumentation is to be used, you should provide specifications for this instrumentation.

Limitations

You should thoroughly discuss the limitations of your assay. We recommend that you include limitations such as the following when appropriate for your device:

- Pregnancy can cause high values of AFP-L3% and AFP.
- Assay results should be interpreted only in the context of other laboratory findings, imaging studies, and the total clinical status of the patient.
- Describe any possible interference from heterophilic antibodies, e.g., human anti-mouse antibodies (HAMA).
- AFP producing tumors other than hepatocellular carcinoma can have high values of AFP-L3% and AFP.
- Samples from acute hepatitis and fulminant hepatitis patients can demonstrate high values of AFP-L3% and AFP.

Performance Characteristics

You should describe the protocol and results for each performance characteristics discussed in Sections 7-9.