Draft Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Herpes Simplex Virus Types 1 and 2 Serological Assays

DRAFT GUIDANCE

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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 Microbiology Devices

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.

Introduction

This special controls guidance document was developed to support the reclassification of the herpes simplex virus types 1 and 2[1] (HSV 1 and 2) serological assays into class II. Herpes simplex virus serological assays are devices that consist of antigens and antisera used in various serological tests to identify antibodies to herpes simplex virus in serum. Additionally, some of the assays consist of herpes simplex virus antisera conjugated with a fluorescent dye (immunofluorescent assays) used to identify herpes simplex virus directly from clinical specimens or tissue culture isolates derived from clinical specimens. The identification aids in the diagnosis of diseases caused by herpes simplex viruses and provides epidemiological information on these diseases. Herpes simplex viral infections range from common and mild lesions of the skin and mucous membranes to a severe form of encephalitis (inflammation of the brain). Neonatal herpes virus infections range from a mild infection to a severe generalized disease with a fatal outcome.

[1] This guidance document addresses assays that detect HSV 1, HSV 2, or both.

This document does not address HSV nucleic acid amplification assays. Please contact the Division of Microbiology Devices in the Office of In Vitro Diagnostic Device Evaluation and Safety for further information on HSV 1 and/or 2 nucleic acid amplification assay submissions.

This guidance is issued in conjunction with a *Federal Register* notice announcing the proposal to reclassify HSV 1 and 2 serological assays as class II. This guidance document is issued for comment purposes only. If a final rule to reclassify these device types is not issued, this guidance document will not be issued as a special control.

Following the effective date of a final rule classifying these devices, any firm submitting a premarket notification (510(k)) for an HSV 1 or 2 serological assay will need to address the risks covered in the special control 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, guidance documents 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 for HSV 1 and 2 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.

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 HSV 1 and 2 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 807 Subpart E, (2) address the specific risks to health associated with HSV-specific antibody or antigen 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 regulations and product codes for HSV 1 and 2 serological assays. (Refer to Section 4 – **Scope.)** In addition, other sections of this guidance document list the risks to health 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 premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the specific content requirements 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).

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 generally 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:

- 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. 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**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

[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.

[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.

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 HSV 1 and 2 serological assays.

Scope

The scope of this document is limited to the following devices as described in 21 CFR 866.3305 with the following product codes:

GQN [Antigen, CD (including CF control), herpesvirus hominis 1, 2]

LKC [Antigens, Indirect hemagglutination (IHA) herpes simplex virus]

GQO [Antisera, CD, herpesvirus hominis 1, 2]

GQL [Antisera, fluorescent, herpesvirus hominis 1, 2]

GQM [Antisera, neutralization, herpesvirus hominis]

LGC [Enzyme linked immunoabsorbent assay, herpes simplex virus]

MXJ [Enzyme linked immunoabsorbent assay, herpes simplex virus, HSV-1]

MYF [Enzyme linked immunoabsorbent assay, herpes simplex virus, HSV-2]

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

§ 866.3305 Herpes simplex virus serological assays.

(a) Identification. Herpes simplex virus serological assays are devices that consist of antigens and antisera used in various serological tests to identify antibodies to herpes simplex virus in serum. Additionally, some of the assays consist of herpes simplex virus antisera conjugated with a fluorescent dye (immunofluorescent assays) used to identify herpes simplex virus directly from clinical specimens or tissue culture isolates derived from clinical specimens. The identification aids in the diagnosis of diseases caused by

herpes simplex viruses and provides epidemiological information on these diseases. Herpes simplex viral infections range from common and mild lesions of the skin and mucous membranes to a severe form of encephalitis (inflammation of the brain). Neonatal herpes virus infections range from a mild infection to a severe generalized disease with a fatal outcome. [Ref. 1,2,3,4].

(b) Classification. The device is classified as class II (special controls) if the herpes simplex virus serological assay is type 1 and/or 2. The device is classified as class III if the herpes simplex virus serological assay is a type other than types 1 and/or 2.

This document does not apply to HSV nucleic acid amplification assays. Please contact the Division of Microbiology Devices in the Office of In Vitro Diagnostic Device Evaluation and Safety for further information on nucleic acid amplification devices.

Risks to Health

Failure of HSV 1 and/or 2 serological assays to perform as indicated or an error in interpretation of results may lead to misdiagnosis and improper patient management [Ref. 5]. The Centers for Disease Control and Prevention (CDC) reports that this failure is seen with nonglycoprotein G-based HSV antibody assays and recommends that glycoprotein G (gG1 or gG2) -based tests be used for type-specific HSV serologic evaluation [Ref. 6].

False positive results may subject pregnant women and newborns to unnecessary treatment with antiviral drugs which could place both the mother and the fetus/infant at risk or lead to an unnecessary cesarean delivery of the fetus [Ref. 7]. False positive results may also lead to potentially toxic therapy in immunocompromised patients who may be at risk for reactivation of latent herpes virus infection and/or disseminated HSV infection [Ref. 8,9,10].

False negative results in pregnant women may lead to neonatal transmission of a primary herpes infection during vaginal delivery which may result in life threatening conditions such as encephalitis [Ref. 7]. False negative results in pre-transplant and/or immunocompromised populations could falsely identify transplant donors which could lead to the transplant of herpes positive organs to nonimmune patients [Ref 2,3,4].

The identified risks are shown in the table below. The measures recommended to mitigate the identified risks are given in this guidance document. You should 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 alternative approaches to address the risk identified in this document, you should provide sufficient detail to support the approach you have used to address the risk.

Identified risk	**Recommended mitigation measures**
Failure of assays to perform as indicated	Sections 6-9
Error in interpretation of results	Section 10

Device Description

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

- a description of the method that your device uses to detect HSV 1 and/or 2 IgM, or IgG or HSV 1 and/or 2 type-specific gG1 or gG2
- a description of the assay components included with the kit
- information on the antigens/antibodies detected or measured
- a clear explanation of 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 assay components, you should include the antigen source and explain how it was characterized. If a recombinant antigen is used, you should supply specific information concerning the specific HSV 1 or 2 epitopes present on the antigen and specific information for antigen characterization. For monoclonal antibodies, you should give specific information concerning HSV 1 or 2 epitopes that will be detected, and provide appropriate antibody characterization.

Performance Characteristics

General Study Recommendations

We recommend that you provide data and statistical evaluation sufficient to determine if the device is safe and effective for all claimed specimen type(s). You should provide data to substantiate claims of intended use or clinical significance, and to validate use of a new technology, as appropriate [Ref. 11].

In general, testing sites should be representative of where the submitter intends to market the device, e.g., clinical laboratory. If the assay is to be used at a point-of-care (POC) setting, we recommend that the clinical and precision studies be conducted at three POC sites with a statistically significant number of specimens from each site.

If the assay is a semiquantitative assay, i.e., it is intended for detection of a significant increase in antibody level between acute and convalescent paired samples, we recommend that you determine the assay linearity over the claimed range, and demonstrate a significant rise in titer between paired samples [Ref. 11].

Please contact the Division of Microbiology Devices in the Office of In Vitro Diagnostic Device Evaluation and Safety for additional information regarding the appropriate data to

substantiate claims of intended use or clinical significance of HSV 1 and/or 2 antigen detection assays.

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 specimen can maintain acceptable performance with your device (e.g., reproducibility at the cutoff) 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. 12].

Precision Testing

You should conduct internal precision testing (i.e., at the manufacturer's site) in accordance with CLSI, EP5-A2 [Ref 13]. Precision testing performed in accordance with CLSI EP15-A2 should be conducted at three external sites [Ref. 14].

We recommend that you characterize samples used for intra- and inter-assay precision testing according to guidelines provided in CLSI, EP12-A [Ref. 15].

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 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-HSV 1 and/or 2
- 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.

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 [Ref. 16]. 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:

- types and levels of interferents tested
- level of antibody in the sample, including a 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 antigens of or antibodies to other relevant microorganisms. In particular, studies should be performed to characterize performance in the presence of antigens of or antibodies to other agents that may clinically be confused with herpes simplex, e.g., Cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes zoster (VZV), *Chlamydia trachomatis, Treponema pallidum*, human papilloma virus (HPV), rubella virus, *Toxoplasma gondii, Candida albicans*, *Neisseria gonorrhea, and* organisms associated with bacterial vaginosis, e.g., *Bacteroides* species, *Gardnerella vaginalis, Mobiluncu*s species. If your antigen and/or antisera are recombinant, we recommend that you provide cross-reactivity studies against the recombinant vector. For HSV 1 and/or 2 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 [Ref. 11].

Cut-off points

We recommend that you provide data to explain how your clinically relevant cut-off point was selected and established. Your cut-off point should distinguish between positive (infected and previously exposed or infected) and negative (non-infected) individuals [Ref. 17]. You should provide information on the use of an equivocal zone for testing. If you believe an equivocal zone is inappropriate, you should explain this carefully.

Other analytical studies

We recommend that you test seroconversion serum panels consisting of well-characterized HSV 1 and 2 samples, which can be obtained from the CDC [Ref.18].

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

Performance of the assay may be demonstrated with multiple matrices by following the design in most current version of CLSI, EP9A2 [Ref. 19].

Prevalence (Expected Values)

We recommend that you establish the prevalence of HSV 1 and/or 2 antibodies and antigen in a population with symptoms consistent with HSV infections or individuals who would be tested for anti-HSV 1 and/or 2 using the new device. You should assay a statistically determined number of samples that are representative of the intended use, clinical utility, and matrix of the samples. You should provide these results based on your new device (rather than a predicate 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.

Method 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 or point-of-care) 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 statistical or clinical differences in the results or populations among sites. Before initiating any clinical study, we suggest you contact the Division of Microbiology Devices.

For type-specific anti-HSV 1 and/or 2 assays you should include a comparison of your device to a well characterized Western blot test, which could be considered "truth" in a clinical study.

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 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 HSV 1 and/or 2 antibody or antigen by comparing test performance with a legally marketed device or by testing against an appropriate algorithm that will diagnose HSV 1 and/or 2 acute and past infection. We recommend prospective collection of specimens from individuals with signs and symptoms consistent with HSV infections or individuals who would be tested for anti-HSV 1 and/or 2 using the new device. 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, appropriate selection, and clinical laboratory characterization of samples being used from a repository bank. You should consider and address potential sources of bias.

Sample Selection, Inclusion, and Exclusion Criteria

We recommend that you evaluate specimens from the intended use population (i.e., individuals with signs and symptoms of herpes simplex 1 and/or 2 infections, prenatal patients, high-risk individuals) in a prospective study, and provide a clear description of how the samples were selected, including reasons that samples were excluded.

The appropriate sample size of the indicated population depends on factors such as precision or reproducibility, interference, variability of your population, standard deviation of results, 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.

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 applicable requirements of 21 CFR 801 and 21 CFR 809.10 before a medical device is introduced into interstate commerce. The following suggestions are aimed at assisting you in preparing labeling that satisfies these requirements.

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 for testing patients. Instructions should 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 specimens 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 or 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 BSL 2 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/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 laboratory findings and the total clinical status of the individual. Timing of specimen collection for paired sera

may be critical. In some patients, antibody titers may rise to significant levels and fall again to lower or undetectable levels within a month. Other patients may not develop significant antibody levels.

We also recommend that you discuss issues concerning interpretation of a nonreactive result in the labeling.

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