

Guidance for Industry and Food and Drug Administration Staff

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

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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

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, (HFA-305), Rockville, MD, 20852. Submit electronic comments to <http://www.regulations.gov>. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. Comments may not be acted upon by the Agency until the document is next revised or updated.

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1. Introduction

This special controls guidance document was developed to support the reclassification of the herpes simplex virus types 1 and 2¹ (HSV 1 and 2) serological assays into class II. HSV 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.

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* final rule announcing the amendment of the special controls for HSV 1 and 2 serological assays.

Designation of this document as a special control means that any firm currently marketing, or intending to market, an HSV 1 or 2 or HSV 1 and 2 serological assay will need to address the issues covered in this special controls guidance. The firm will need to show that its device addresses the issues of safety and effectiveness identified in this guidance, either by meeting the recommendations of this guidance or by some other means that provide equivalent assurances of safety and effectiveness.

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

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 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 FD&C 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 regulation and product codes for HSV 1 and 2, also known as Human Herpes Viruses types 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/MedicalDevices/DeviceRegulationandGuidance/default.htm>

3. Abbreviated 510(k) Submissions

As explained in “**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance,**” <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm>, a manufacturer may submit either a Traditional 510(k) or an Abbreviated 510(k). An Abbreviated 510(k) provides a means to streamline the review of data in a 510(k) through a reliance on FDA-recognized consensus standards, special controls, or FDA guidance documents. Guidance on the content and format for abbreviated and traditional 510(k)s is available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm>. Also, see Section 514(c)(1)(B) of the FD&C Act and the FDA guidance, “**Use of Standards in Substantial Equivalence Determinations,**” <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm>

4. 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, CF (including CF control), herpesvirus hominis 1, 2]

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

- GQO** [Antisera, CF, 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 rule FDA has identified these devices, classified under 21 CFR 866.3305 as follows:

(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.

(b) *Classification.* Class II (special controls). The device is classified as class II (special controls). The special control for the device is FDA's revised guidance document entitled "Class II Special Controls Guidance Document: Herpes Simplex Virus Types 1 and 2 Serological Assays." For availability of the guidance revised document, see §866.1(e).

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.

5. Risks to Health

Failure of HSV 1 and/or 2 type specific 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) reported 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 8-10].

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 risks identified in this document, you should provide sufficient detail to support the approach you have used to address the risks.

Identified risk	Recommended mitigation measures
Failure of assays to perform as indicated	Sections 6-9
Error in interpretation of results	Section 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 HSV 1 and/or 2 IgM, or IgG or HSV 1 and/or 2 type-specific IgM or IgG.
- 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 and purification. For monoclonal antibodies, you should give specific information concerning HSV 1 or 2 epitopes that will be detected, and provide appropriate antibody characterization and purification.

7. 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 sufficient number of specimens at each site so that results will be statistically meaningful.

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. You should 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 in CLSI EP7-A [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), Varicella-zoster Virus (VZV), *Chlamydia trachomatis*, *Treponema pallidum*, human papilloma virus (HPV), rubella virus, *Toxoplasma gondii*, *Candida albicans*, *Neisseria gonorrhoea*, and organisms associated with bacterial vaginosis, e.g., *Bacteroides* species, *Gardnerella vaginalis*, *Mobiluncus* 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 using the most current version of CLSI, EP9A2 [Ref. 19].

8. 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.

9. 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.

So that acceptance criteria or data summaries can be best interpreted during the review, we recommend that you provide appropriate specific information concerning protocols. This 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 antibody, by devices that do not differentiate HSV 1 or 2 by comparing test performance with a legally marketed device or by testing against an appropriate algorithm that will diagnose HSV acute and past infections. To determine seroconversion, acute and convalescent serum should be collected during the acute stage of infection and by collecting a second sample 10-14 days later.

For establishing performance of type-specific anti-HSV, 1 and/or 2 IgG assays you should compare your device to a well-characterized western blot, immunoblot or an FDA cleared immunoblot in a clinical study. Well-characterized western and immunoblots have established a uniform high sensitivity and ability to discriminate HSV 1 and HSV 2 antibodies [Ref. 5]. We consider these methodologies as reference methods for type specific HSV 1 and/or 2 assays. You may report the sensitivity and specificity of your device when comparing its performance to any of these methods.

For antigen detection assays, we recommend that you compare the performance of your device to virus isolation by culture as a reference method.

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 in a prospective study, and provide a clear description of how the samples were selected, including reasons that samples were excluded. Target populations include individuals with signs and symptoms of HSV 1 and/or 2 infections, pregnant women and sexually active adults at risk for sexually transmitted diseases.

Assessment of the device's performance in low prevalence populations is required to assist in determining the specificity of the device.

Low prevalence populations are not a target population for HSV testing, as the public health benefit of screening for HSV in low prevalence populations has not been determined [Ref. 5].

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.

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 applicable 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 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 overall clinical status of the individual. Timing of specimen collection for paired or non 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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