Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Serological Reagents for the Laboratory Diagnosis of West Nile Virus

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Food and Drug Administration
Center for Devices and Radiological Health

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

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to Docket No. 2003D-0303. 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 document was developed as a special control to support the classification of the West Nile virus (WNV) serological reagents into class II (special controls). West Nile virus serological reagents are devices that consist of antigens and antisera for the detection of anti-West Nile virus IgM antibodies, in human serum, from individuals that have signs and symptoms consistent with viral meningitis/encephalitis. The detection aids in the clinical laboratory diagnosis of viral meningitis/encephalitis caused by West Nile virus. The device is intended for use in the presumptive diagnosis of patients in conjunction with other clinical and laboratory findings.

This guidance is issued in conjunction with a *Federal Register* notice announcing the classification of the West Nile virus serological reagents.

Following the effective date of a final rule classifying the device, any firm submitting a 510(k) premarket notification for a West Nile Virus serological assay 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 comply with 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: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM588914.pdf.

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 West Nile Virus 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 & 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 West Nile virus serological reagents identified in this guidance and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device, unless exempt from the premarket notification requirements of the Act (refer to 21 CFR 807.85).

This guidance document identifies the classification regulations and product codes for West Nile virus serological reagents (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 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.

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**[1]," 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

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

demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

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

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

Coversheet

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

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 8 for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary report

We recommend that the summary report contain:

- 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]

- Description of device design requirements.

- 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 for the recommended format.

(Refer to Section 5 for the risks to health generally associated with the use of this device that FDA has identified).

- 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 6 and 7 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 any part of the device design or testing relies on a recognized standard, (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] Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. (21 USC 514(c)(2)(B)). For more information, refer to 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

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

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

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.

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 866.3940 (product code: NOP):

The classification identification below identifies the device as it existed at the time of classification.

> West Nile virus serological reagents are devices that consist of antigens and antisera for the detection of anti-West Nile virus IgM antibodies, in human serum, from individuals who have signs and symptoms consistent with viral meningitis/encephalitis. The detection aids in the clinical laboratory diagnosis of viral meningitis/encephalitis caused by West Nile virus.

5. Risks to Health

There are no known *direct* risks to patient health. However, failure of the test to perform as indicated or error in interpretation of results may lead to improper patient management. Therefore, use of assay results to adjust a treatment regimen without consideration of other clinical factors could pose a risk. A false negative measurement can result in continued treatment with toxic agents for non-West Nile virus viral encephalitis or bacterial meningitis. Geriatric patients are particularly susceptible to the nephrotoxic effects of antiviral agents, used for the treatment of viral encephalitis, and vancomycin, used for empiric treatment of bacterial meningitis. A false positive measurement can result in discontinuation of otherwise appropriate treatment for non-West Nile virus viral encephalitis or bacterial meningitis.

In the table below, FDA has identified the risks to health generally associated with the use of West Nile virus serological reagents 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
Improper patient management	Section 6, 7, and 8

6. Performance Characteristics

General Study Recommendations

We recommend that you include a description of the method used to detect West Nile virus antibodies and of the reagent components in the kit. Whenever possible, we recommend that you include patient samples derived from the intended use population (e.g., patients with signs and symptoms of meningioencephalitis) for the analytical protocols described below.

FDA recommends that you evaluate your assay in at least two external sites in addition to that of the manufacturer. Generally, we recommend that performance be assessed 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 separately to evaluate any inter-site variation and include results of the analysis in the 510(k) summary report. You can pool clinical study 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 any clinical study, you may contact the Division of Microbiology Devices.

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

Information should be provided on the antibodies detected or measured, on the methodology used for measurement, and on the technology used. Information should include a clear explanation for what controls and calibrators are to be used in the assay and how these perform.

Specific Performance Characteristics

Reproducibility

We recommend that you characterize intra- and inter-assay reproducibility using patient samples and quality control materials according to guidelines provided in "Evaluation of Precision Performance of Clinical Chemistry Devices;" Approved Guideline (1999) National Committee for Clinical Laboratory Standards (NCCLS), Document EP5-A and "User Protocol for Evaluation of Qualitative Test Performance;" Approved Guideline (2002) National Committee for Clinical Laboratory Standards (NCCLS), EP-12A. These documents includes guidelines for experimental design, computations, and a format for stating performance claims. We recommend that you evaluate reproducibility at relevant measurements, including levels near medical decision points and measurements near the limits of the reportable range.

We recommend that you include the items listed below:

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

We recommend that you identify which factors (e.g., instrument calibration, reagent lots, operators) were held constant, which were varied during the evaluation, and describe the computational methods, if they are different from that described in NCCLS EP5-A and EP12-A.

Interference

We recommend that you characterize the effects of potential interferents on assay performance. Examples of experimental designs, including guidelines for selecting interferents for testing, are described in detail in "Interference Testing in Clinical Chemistry; Approved Guideline" (2002) National Committee for Clinical Laboratory Standards, Document EP7-A. Potential sources of interference can include compounds normally found in serum, such as other class antibodies (i.e., IgM or IgG), triglycerides, hemoglobin, bilirubin, and lipids.

We recommend that you include the following items:

- types and levels of interferents tested
- antibody level in the sample
- number of replicates tested
- definition or method of 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 the criteria or level on which non-interference is determined.

You may not need to perform additional interference testing with potential interferents identified in literature or by other sources. However, we recommend that you include them in the labeling.

Cross reactivity

We recommend that you include data on the assay specificity by measuring the cross reactivity of your device with other relevant microorganisms. In particular, studies

should be performed to characterize performance in the presence of other flaviviruses (e.g., St. Louis encephalitis, dengue virus, yellow fever, Japanese encephalitis), alphaviruses (e.g., eastern equine encephalitis), and other viruses that cause meningioencephalitis symptoms (e.g., enteroviruses, herpes simplex).

Cut-Off Points

We suggest that data be furnished to explain how the cut-off point was selected and established. If appropriate, information should be provided on the use of an equivocal zone for testing. If data suggests that an equivocal zone is not appropriate, this should be carefully explained.

Other analytical studies

See FDA Guidance Document "Review Criteria for IgM Antibodies for Viral Agents, 8/1/92"

7. Method Comparison

Clinical Sensitivity and Comparative Performance

FDA recommends that you determine clinical sensitivity by comparing test performance against patients with characterized disease confirmed using established laboratory tests such as the Plaque Reduction Neutralization Test or using current CDC guidelines for diagnosis of this disease. While prospective samples are preferred, well characterized data banks can be used as the source for samples. There should be clear information supporting sample integrity and demonstrating appropriate selection and characterization of samples being used from a repository bank. Sources of bias should be considered and addressed.

We recommend that you evaluate the prevalence of West Nile virus antibodies by your assay in an endemic area, and analyze the data according to demographic variables (e.g., age, sex).

In the absence of clinical information, samples may be studied based on comparative serological results using reference serologic screening tests with appropriate confirmatory tests. These results should be reported as percent agreement rather than sensitivity.

Clinical Specificity

FDA recommends that for West Nile virus serological reagents you evaluate clinical specificity of your device in patients drawn from the endemic normal population. Patients with febrile and neurological disease should be included to ensure that test performance is properly challenged.

Specimen collection and handling conditions

We recommend that you substantiate statements in your labeling about specimen storage and transport by assessing whether the device can maintain acceptable performance (e.g., reproducibility) over the storage times and temperatures recommended to users. For example, an appropriate study may include an analysis of aliquots stored under the conditions of time, temperature, or specified number of freeze/thaw cycles. We recommend that you state the criteria for an acceptable range of recoveries under the recommended storage and handling conditions [see "Procedures for Handling and Processing of Blood Specimens;" Approved Guideline (1990) National Committee for Clinical Laboratory Standards (NCCLS), Document H18-A]

Sample selection, inclusion and exclusion criteria

We recommend that you evaluate patient samples from the intended use population (i.e., patients with signs and symptoms of meningitis/encephalitis), and provide a clear description of how the samples were selected, including reasons that samples are excluded.

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

Presentation of results

When providing the results of your study, we recommend that you demonstrate the association between West Nile virus serological results and the results of clinical case definitions for preliminary and confirmed West Nile virus infections as defined by the current CDC guidelines [http://www.cdc.gov/ncidod/dvbid/westnile/clinical_guidance.htm]. We recommend that you stratify data by important demographic factors (e.g., age and sex) if the factors have the potential to bias the results.

8. 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 the requirements of 21 CFR 807.87(e).[5]

Directions for use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR 807.87(e), we expect to see

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

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 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.

Precautions for interpretations

We recommend that you address the limitations of your assay with statements in the labeling, such as:

- Serological test results are presumptive and require confirmation by Plaque Reduction Neutralization Test or using the current CDC guidelines for diagnosis of this disease.
- Testing should only be performed on patients with clinical symptoms of meningitis/encephalitis. This test is not intended for screening the general population. The positive predictive value depends on the likelihood of the virus being present.
- Results from immunosuppressed patients must be interpreted with caution.
- Serological cross-reactivity across the flavivirus group is common (i.e., between St. Louis encephalitis, dengue 1, 2, 3 & 4; Murray Valley encephalitis, Japanese encephalitis, and yellow fever viruses).
- IgM antibodies may persist for more than 500 days in up to 60% of cases. Positive results should be interpreted in the context of clinical and other laboratory findings and may not indicate active West Nile virus induced disease.
- Assay results should be interpreted only in the context of other laboratory findings and the total clinical status of the patient.