

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. 2006D-0347]

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Certifier L. C. Lawson  
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**Draft Guidance for Industry and Food and Drug Administration Staff; In Vitro Diagnostic Multivariate Index Assays; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a revised draft guidance entitled “In Vitro Diagnostic Multivariate Index Assays.” FDA is issuing this revised draft guidance to address the definition and regulatory status of a class of In Vitro Diagnostic Devices referred to as In Vitro Diagnostic Multivariate Index Assays (IVDMIA). The revised draft guidance also addresses premarket and postmarket requirements with respect to IVDMIA. The initial draft of this guidance was issued September 7, 2006.

**DATES:** Submit written or electronic comments on this draft guidance by [*insert date 30 days after date of publication in the Federal Register*].

**ADDRESSES:** Submit written requests for single copies of the draft guidance document entitled “In Vitro Diagnostic Multivariate Index Assays” to the Division of Small Manufacturers, International, and Consumer Assistance (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850 or to the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration,

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1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your request, or fax your request to 240–276–3151. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the draft guidance.

Submit written comments concerning this draft guidance to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. Identify comments with the docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Courtney Harper, Center for Devices and Radiological Health (HFZ–440), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 240–276–0694.

*For further information concerning the guidance as it related to devices regulated by CBER:* Martin Ruta, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–3518.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In the **Federal Register** of September 7, 2006 (71 FR 52800). FDA published a notice of availability of the initial draft guidance to address the definition and regulatory status of a class of in vitro diagnostic devices referred to as “In Vitro Diagnostic Multivariate Index Assays (IVDMIAAs).” The initial draft guidance also addressed premarket and postmarket requirements with respect to IVDMIAAs.

An IVDMIA, as defined in the draft guidance document, is a device within the meaning of the Federal Food, Drug, and Cosmetic Act (the act). Some

IVDMIAAs are laboratory-developed tests (LDTs); laboratory-developed IVDMIAAs are a specific subset of LDTs. While FDA has stated that “clinical laboratories that develop (in-house) tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the Act,” 62 FR <sup>(November 21, 1997)</sup> 62249, the agency has generally exercised enforcement discretion over most standard LDTs. However, in the draft guidance, FDA recognizes that IVDMIAAs include elements that are not among the primary ingredients of standard LDTs (e.g., complex, unique, interpretation functions). IVDMIAAs thus do not fall within the scope of LDTs over which FDA has generally exercised enforcement discretion.

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IVDMIAAs raise significant issues of safety and effectiveness. These types of tests are developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratorians, and clinicians who order these tests. Additionally, IVDMIAAs frequently have a high risk intended use. FDA is concerned that patients and healthcare practitioners are relying upon IVDMIAAs with high risk intended uses to make critical healthcare decisions without any independent assurance that the IVDMIA has been properly clinically validated, and without any ability to assess whether the test yields clinically valid results.

With this revised draft guidance document, FDA seeks to identify IVDMIAAs as a discrete category of device, and to clarify that, even when offered as LDTs, IVDMIAAs must meet pre- and post-market device requirements under the act and FDA regulations, including premarket review requirements in the case of most class II and III devices.

FDA received and considered approximately 60 sets of comments on the initial draft guidance document, including comments provided at a public

meeting that was held on February 8, 2007. After taking the comments into consideration, the FDA has updated the draft guidance document to provide clarifications as needed.

Certain comments on the initial draft guidance document requested that FDA undertake notice and comment rulemaking rather than issue a guidance document in order to allow sufficient opportunity for public input. In response to this concern, FDA extended the comment period on the draft guidance document from 90 days to 180 days, March 5, 2007 (71 FR 68822), and held a public meeting to provide a forum for presentations and comments on the draft guidance document. The meeting was attended by 266 people representing a cross-section of interested stakeholders including industry, consumer groups, and the medical community. FDA has carefully considered the comments it has received. Many comments reflect that stakeholders construed the definition of IVDMIAs in the initial draft guidance document to encompass a wider range of tests than FDA had intended. The initial draft guidance document has been revised to clarify the definition of an IVDMIA and to provide examples of tests that the agency does and does not consider to be IVDMIAs. This section of the draft guidance was modified so that stakeholders can more easily understand the nature of tests designated as IVDMIAs, and manufacturers can more easily determine whether their tests are IVDMIAs. However, the clarifications do not alter the scope or intent of the definition of an IVDMIA found in the initial draft guidance document.

In response to additional comments received, the revised draft guidance document now clarifies FDA regulatory mechanisms in general, such as how devices are classified and reviewed based on the risk of the intended use, how laboratory-developed IVDMIAs should be labeled, and how manufacturers can

update and improve cleared or approved devices using existing mechanisms within the regulatory framework. These existing mechanisms enable manufacturers to bring innovative new tests to the market and ensure that they can be updated and improved as new scientific information becomes available. While this information is generally available in existing regulations, guidance documents, and on the FDA Web site, the revised draft guidance provides a summary of this information with a focus on IVDMIAs in order to assist those stakeholders who are not familiar with existing FDA requirements.

In other comments, some stakeholders expressed concern that requiring FDA regulatory compliance for IVDMIAs has the potential to discourage the development of new tests for rare diseases. A manufacturer of an IVDMIA for a disease or condition that affects small patient populations may find that research and development costs exceed market returns. The draft guidance has been revised to indicate FDA's intent to exercise enforcement discretion for laboratory-developed IVDMIAs that are intended to diagnose rare diseases (i.e., IVDMIAs that meet the definition of Humanitarian Use Devices under 21 CFR part 814 Subpart H).

Finally, the draft guidance document clarifies that laboratories that manufacture IVDMIAs should follow the Medical Device Reporting requirements for manufacturers, 21 CFR part 803 for their IVDMIA device(s). As in the initial draft guidance, the revised draft guidance indicates that FDA intends to issue guidance to assist laboratories that manufacture IVDMIAs in complying with the Quality System regulation (QS), 21 CFR part 820. In response to comments that expressed concern about coming into compliance with the QS regulation, the revised draft guidance indicates that until such a final guidance is published, FDA intends to exercise enforcement discretion

with regard to post-market QS requirement enforcement for laboratories that manufacture IVDMIAAs, recognizing that some Clinical Laboratory Improvement Amendments of 1988 (CLIA' 88) requirements may partially fulfill corresponding QS regulation requirements.

FDA is issuing this revised draft in order to gather significant new comments before issuing a final version of the guidance. Because the agency believes it has addressed the most important concerns raised by the comments it received on the initial draft, and because it is important to issue a final guidance to provide clarity for stakeholders, FDA is providing a comment period of 30 days following publication of this document.

## **II. Significance of Guidance**

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance represents the agency's current thinking on IVDMIAAs. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

## **III. Electronic Access**

Persons interested in obtaining a copy of the draft guidance may do so by using the Internet. To receive "In Vitro Diagnostic Multivariate Index Assays," you may either send an e-mail request to *dsmica@fda.hhs.gov* to receive an electronic copy of the document or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number 1610 to identify the guidance you are requesting.

CDRH maintains an entry on the Internet for easy access to information including text, graphics, and files that may be downloaded to a personal computer with Internet access. Updated on a regular basis, the CDRH home

page includes device safety alerts, **Federal Register** reprints, information on premarket submissions (including lists of approved applications and manufacturers' addresses), small manufacturer's assistance, information on video conferencing and electronic submissions, Mammography Matters, and other device-oriented information. The CDRH Web site may be accessed at <http://www.fda.gov/cdrh>. A search capability for all CDRH guidance documents is available at <http://www.fda.gov/cdrh/guidance.html>. Guidance documents are also available on the CBER Internet site at <http://www.fda.gov/cber/guidelines.htm> or on the Division of Dockets Management Internet site at <http://www.fda.gov/ohrms/dockets>.

#### **IV. Paperwork Reduction Act of 1995**

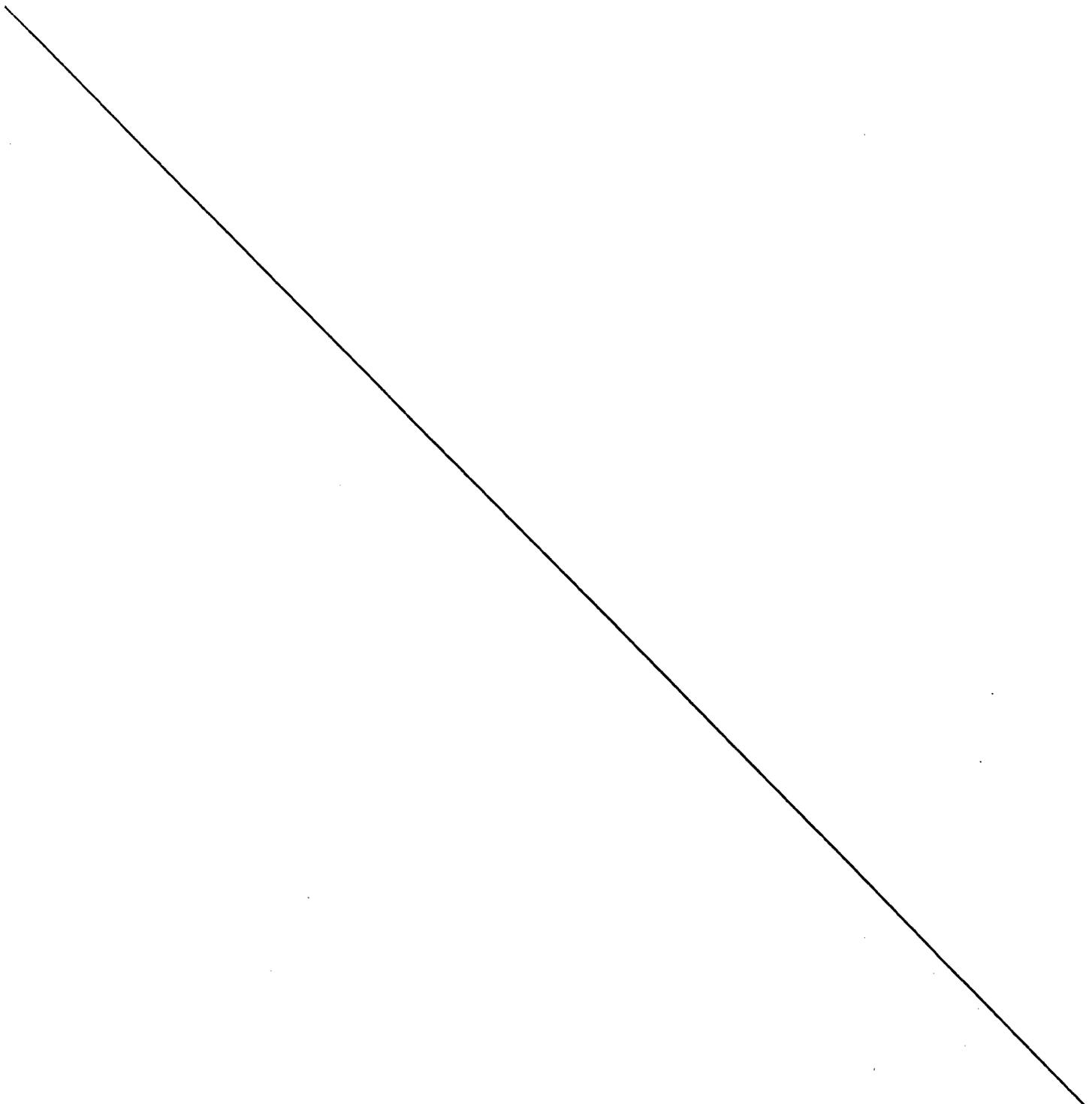
This draft guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collections of information in the draft guidance document have been approved by OMB in accordance with the PRA under the regulations governing premarket notifications (21 CFR part 807, subpart E, OMB control number 0910–0120) premarket approval applications (21 CFR part 814, OMB control number 0910–0231), investigational device exemptions (21 CFR part 812, OMB control number 0910–0078), quality system regulation (21 CFR part 820, OMB control number 0910–0073), and medical device reporting (21 CFR part 803, OMB control number 0910–0437). The labeling provisions addressed in this guidance have been approved by OMB under OMB control number 0910–0485.

#### **V. Comments**

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**), written or electronic comments regarding this document on or before *[insert date 30 days after date of publication in the **Federal Register**]*.

Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

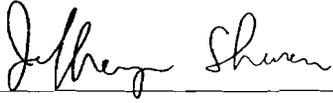
Submit two paper copies of any mailed comments, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments



received may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated:           JUL 20 2007          

July 20, 2007.



Jeffrey Shuren,  
Assistant Commissioner for Policy.

[FR Doc. 07-????? Filed ??-??-07; 8:45 am]

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