Guidance for FDA Staff

# Regulating *In Vitro* Diagnostic Device (IVD) Studies

**Document issued on: December 17, 1999**

**U.S. Department Of Health And Human Services**
**Food and Drug Administration**
**Center for Devices and Radiological Health**
**Office of Compliance**
**Division of Bioresearch Monitoring**

# Preface

## Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to, Food and Drug Administration, Center for Devices and Radiological Health, Division of Bioresearch Monitoring, (HFZ-312), 2094 Gaither Road, Rockville, Maryland 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Viola Sellman at (301) 594-4723.

## Additional Copies

World Wide Web/CDRH/ home page: http://www.fda.gov/cdrh/comp/ivdreg.html or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 1132 when prompted for the document shelf number.

# Regulating *In Vitro* Diagnostic Device (IVD) Studies[1]

## Purpose

This document is intended to provide guidance for the Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, concerning regulation of in vitro diagnostic (IVD) device studies. The guidance explains how the Office of Compliance, Division of Bioresearch Monitoring (DBM), in conjunction with the Office of Device Evaluation (ODE), interprets and enforces the statute and regulations for investigational studies that involve the use of IVD's.

**DEFINITION**

In vitro diagnostics:

IVD's are reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body [21 CFR 809.3(a)]. IVD's are devices, as defined in section 201(h) of the Act, and may also be biological products subject to section 351 of the Public Health Service Act.

**INVESTIGATIONAL STUDIES OF IVD's:**

Exempt Studies:
IVD's may be exempt from IDE requirements if certain conditions are met:

1) the testing is non-invasive;
2) does not require invasive sampling presenting significant risk;
3) does not introduce energy into a subject; and
4) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic device or procedure (21 CFR 812.2(c)(3)).

[1]This document is intended to provide guidance. It represents the Agency's current thinking on the above. 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, regulations, or both.

In addition, IVD's exempt from the IDE regulation must comply with the labeling requirements that require a statement, as applicable in each case: "For Research Use Only. Not for use in Diagnostic procedures", or "For Investigational Use Only. The performance Characteristics of this product have not been established." (21 CFR 809.10(c)(2)). Another important regulatory aspect to remember is that Exempt Studies of IVD's do not cover activities that involve the disqualification of a clinical investigator (21 CFR 812.119).

Non-Exempt Studies:

Studies exempt from IDE requirements may or may not be exempt from IRB review and approval, or from the need to comply with informed consent requirements. (See 21 CFR Parts 56 and 50, respectively.) For example, if the testing is invasive and the results are reported back to the subject/patient, then IDE, IRB and informed consent requirements apply. Compliance with IRB and informed consent regulations depends upon the purpose and nature of the study and should be evaluated accordingly. For example, if a study involving leftover blood samples or previously collected samples, i.e., retrospective from patients that had undergone prostate surgery, then IRB approval and informed consent would be required. However, if the source of a leftover sample or a previously collected sample were unknown, then informed consent rules would not be applicable. Research involving human biological materials has the potential to uncover detailed medical and genetic information about a specific person. The use of linked or coded biological materials can be traced to a specific person by name or patient number and, therefore, is considered human subject research.

Exemption from IDE regulatory requirements does not relieve the sponsor from establishing and implementing distribution controls and proper labeling practices that ensure the use is consistent with the device's investigational or research purpose. Labeling requirements are discussed in the next section.

The provisions regarding disqualification of investigators apply to all clinical investigations of devices, including those that do not require FDA approval of an IDE. The clinical investigator disqualification regulation criteria found in 21 CFR 812.2 is not intended to eliminate the responsibility of clinical investigators of devices to follow procedures and standards associated with good scientific practice. (62 FR 12087) Whether or not an investigation requires an IDE, a clinical investigator's work that may be considered in connection with a marketing application is expected to comply with the FDA's regulations and scientific standards relating to informed consent, IRB oversight, inspections, adherence to investigational protocols, and pertinent reports and record-keeping. These scientific and regulatory expectations extend to the sponsors when they engage in clinical studies.

## LABELING

Investigational Use Only (IUO)**:**
IVD's that are exempt from the IDE requirements of Part 812 must be labeled: "For Investigational Use Only. The performance characteristics of this product have not been established." (21 CFR 809.10(c)(2)(ii))

Research Use:

IVD's intended for research use are devices in a laboratory-based phase of development. Laboratory research may use animal or human tissues. A research device may not be used for human clinical diagnostic or prognostic use. Tests performed with in vitro products intended for research use should be used only in a preclinical or nonclinical setting and the labeling must state: "For research use only. Not for use in diagnostic procedures." (21 CFR 809.10(c)(2)(i))

## INSPECTIONAL AUTHORITY

Section 704 of the Federal Food, Drug, and Cosmetic Act (the Act) gives FDA the authority to inspect facilities where devices are "manufactured, processed, packed or held."

## WARNING vs. UNTITLED LETTER

FDA's Regulatory Procedures Manual (RPM) states that Warning Letters should issue for violations of regulatory significance only. Generally, if a sponsor's or investigator's actions warrant written notification but there are no charges on which to base a Warning Letter, an untitled letter may be issued. For a Warning Letter, adulteration and misbranding charges may be based on violations such as failure to obtain informed consent and/or institutional review board approval prior to the time subjects participated in an investigational study (21 CFR Parts, 812, 50 and 56.) Charges based on failure to comply with IDE requirements, except for the disqualification of a clinical investigator, ordinarily will not be applicable in cases where the device meets IDE requirements, as discussed above in this guidance in the "Exempted Studies" section. However, should an unusual case arise, DBM may consider regulatory options, in consultation with the Office of Chief Counsel (OCC), OC, and ODE management, before a final decision is made.

## OTHER ACTION BY DBM

Based on the review of the establishment inspection report and/or other documentation, DBM may recommend to ODE that an investigator's data not be considered during the review of a submission. ODE may then make the determination whether to reject the data and/or deny the application based on the information provided by DBM from the inspection report.

## CONCLUSION

In summary, in vitro diagnostic devices are not required to satisfy the IDE requirements provided they meet the labeling and other requirements identified in the "Exempt Studies" section of this guidance. The sponsor and/or clinical investigator are not exempt from the requirements; but these requirements may not always be applicable. The IDE exemption for research use and investigational use IVD's does not preclude the need for valid scientific data from a properly conducted clinical investigation in support of a marketing application (510(k) or PMA) submitted to FDA. Accordingly, DBM may recommend to ODE, when appropriate, that the investigators' data not be considered during the review. ODE may then make the determination whether to reject the data and/or deny the application.