# FDA Compliance Policy Guide (CPG) - Draft

**Chapter 3 - Devices**

**Sub Chapter 300 - General / Processes**

**Title: Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only - Draft**

**Date Draft released: January 5, 1998**

This draft guidance document represents the agency's current thinking on commercialization of in vitro diagnostic devices labeled for research use only or investigational use only. 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.

Interested persons may submit by April 6, 1998 to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, room 1-23, Rockville, Maryland 20857 written comments on the draft CPG entitled "Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only." Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Federal Register docket number [97D-0506]

The agency will review all comments, but in issuing a final CPG, need not specifically address every comment. The agency will make changes to the CPG in response to comments, as appropriate. A copy of the draft CPG and received comments may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

For questions regarding this draft document, contact Betty W. Collins, Office of Compliance (HFZ-300), Center for Devices and Radiological Health, Food and Drug Administration, 2098 Gaither Road, Rockville, MD 20850, (301)594-4588, ext 165.

U.S. Department of Health
and Human Services
Food and Drug Administration
Office of Regulatory Affairs
Office of Enforcement
Division of Compliance Policy

**Chapter 3 - Devices**

**Sub Chapter 300 - General / Processes**

**Title: Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only - Draft**

**Date Draft released: January 5, 1998**

BACKGROUND:

The Investigational Device Exemptions (IDE) regulations (Title 21, Code of Federal Regulations (CFR), Part 812) require prior Food and Drug Administration (FDA) approval of clinical investigations intended to establish the safety and effectiveness of significant risk devices. Manufacturers may conduct certain categories of investigations without filing an IDE application if certain requirements set forth in 21 CFR 812.2(b) are met.

In vitro diagnostic devices (IVD's) may be exempt from IDE requirements if certain conditions are met: the testing is non-invasive, does not require invasive sampling presenting significant risk, does not introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure (21 CFR 812.2(c)(3)). In addition, to be exempt from the IDE regulation, IVD's must comply with 21 CFR 809.10(c)(2), which requires that the labeling for research and investigational devices state, 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."

Many manufacturers of IVD's have not followed the requirements set forth in 21 CFR Parts 809 and 812. As a result, numerous IVD's labeled for research or investigational purposes are being promoted, distributed, and used for purposes other than research or investigation. This commercialization has resulted in the widespread use of laboratory tests with unproven performance characteristics. Use of such tests may mislead providers of medical diagnosis and treatment and cause serious adverse health consequences to unknowing patients.

Unless exempted from the requirement to submit a premarket notification under Section 510(k), IVD's that are commercially distributed for diagnostic use prior to Agency clearance or approval are adulterated and misbranded under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(f)(1)(B) and 352(o)). Such distribution subjects the devices and responsible firms to regulatory action. This is true even if the IVD's are labeled in accordance with 21 CFR 809.10(c) and are used in combination with other medically accepted diagnostic devices or procedures.

PURPOSE:

This Compliance Policy Guide (CPG) provides guidance on FDA's enforcement priorities concerning investigational or research IVD's that are being commercialized for diagnostic or prognostic purposes.

Additionally, this draft CPG does not pertain to in vitro products whose use is limited to laboratory research that is entirely unrelated to the development of IVD's.

POLICY:

This policy is applicable to IVD's that are regulated by the FDA's Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER). This CPG applies to IVD's that are sold or distributed as test kits. However, this CPG does not pertain to analyte specific reagents (ASR's) that are sold and used in accordance with 21 CFR 809.10(e), 809.30, and 864.4020.

IVD's labeled "For Investigational Use" are commercialized, in violation of the Federal Food, Drug, and Cosmetic Act (the Act), if they are labeled or promoted with statements indicating the devices are safe or effective for in vitro diagnostic use prior to Agency clearance or approval (21 U.S.C. 352(a), 351(f)(1)(B), and 352(o)).

Devices labeled "For Research Use" are mislabeled if the device is being used for investigational purposes, i.e., in a clinical study, even if involving only one subject, where the diagnostic or prognostic measurement will be reported to the patient's physician or medical records or will be used to assess the patient's condition, regardless of whether or not confirmatory tests or procedures are used. Research use is limited to the initial research phase of product development that is necessary to identify test kit methods, components, and analytes to be measured or to laboratory research that is entirely unrelated to product development. See 21 CFR 809.10(c)(2)(I).

However, the Agency recognizes that certain improperly commercialized IVD's have been in extensive clinical use for a significant period of time. The Agency further recognizes that immediate regulatory action against certain of these IVD's might result in adverse consequences to individual patients and the public health. Therefore, FDA is publishing this CPG in order to describe the Agency's enforcement policy, which includes the Agency's intention to exercise discretion for designated periods of time, so as not to cause undue disruption to the possibly beneficial use of IVD's that have not received Agency clearance prior to commercialization.

Except as provided below under Enforcement Priority Category I, FDA intends to prioritize its enforcement actions based on how long the product has been improperly commercialized. Firms that have commercialized IVD's for relatively long periods of time should be able to undertake investigations and generate data more quickly than firms that have begun to commercialize their IVD's more recently.

Accordingly:

For devices that have been in use for more than 10 years, the Agency intends to exercise its enforcement discretion to permit IVD manufacturers, importers and distributors up to 18 months from the *Federal Register* publication date of the Notice of Availability (NOA) for this CPG to obtain Agency approval of a premarket approval (PMA) application or product license application (PLA) or clearance of a Section 510(k) (premarket notification) submission.

For devices that have been in use 5 to 10 years, the Agency intends to exercise its enforcement discretion to permit IVD manufacturers, importers and distributors up to 24 months to obtain the necessary PMA/PLA approvals or 510(k) clearances.
For devices that have been in use for less than 5 years, the Agency intends to exercise its enforcement discretion to permit IVD manufacturers, importers and distributors up to 30 months to obtain the necessary PMA/PLA approvals or 510(k) clearances.

FDA intends the exercise of its enforcement discretion, under this timetable, to be contingent on firms taking the necessary steps to obtain the requisite approvals or clearances, including undertaking, within six months of the publication of the NOA for this CPG, any necessary clinical investigations or other studies under a protocol sufficient to allow determination of the IVD's safety and effectiveness.

The FDA believes that the 18 to 30 month time period that begins with the publication date of the NOA for this CPG is a reasonable period for gathering safety and effectiveness data and obtaining Agency review for clearance or approval.

During this 18 to 30 month time period, FDA intends to exercise its enforcement discretion against improperly commercialized IVD’s as follows:

<u>Enforcement Priority Category I</u>

IVD’s that meet the following criteria will constitute FDA's highest enforcement priority. FDA intends to take immediate regulatory action to remove such violative commercialized devices from the marketplace. The following types of unapproved commercialized IVD’s fall into FDA's Enforcement Priority Category I:

1. IVD’s meeting all the criteria of a, b, and c, as listed below:

    a. the IVD is being used as a stand alone test for diagnostic, monitoring, or screening procedures, and

    b. the test result may lead to a significant medical decision or intervention (e.g., organ removal, surgery, radiation therapy, chemotherapy, drug treatment with potentially severe toxicity, or quarantine), and

c. there is a significant question as to the IVD's safety and effectiveness, as demonstrated by the review of scientific literature or by an assessment of standards of accepted medical practice; or

2. IVD's used for diagnosis or prognosis in humans for which there are no data on human use or only anecdotal data to support safety and effectiveness of the device, as determined by FDA; or

3. Any IVD previously in Enforcement Priority Category II whose manufacturer, importer, or distributor:

a. fails to comply with the labeling requirements of 21 CFR 809.10(c) within three months of the publication date of the NOA for this CPG; or

b. fails to commence, within six months of the publication date of the NOA for this CPG, a clinical or scientifically valid study under a protocol sufficient to allow determination of the IVD's safety and effectiveness; or

c. fails to obtain PMA or PLA approval or Section 510(k) clearance within the 18 to 30 month time period of the publication date of the NOA for this CPG.

Enforcement Priority Category II

Category II includes all improperly commercialized IVD's that are not identified in Enforcement Priority Category I. During the 18 to 30 month time period following the publication of the NOA for this CPG, FDA intends to exercise its enforcement discretion with respect to IVD's in Enforcement Priority Category II, and refrain from instituting regulatory action if a firm can document its efforts to collect data for submission of Section 510(k) notifications, PMA applications, or PLA's within the 18 to 30 month time period.

Manufacturers, importers, and distributors of IVD's that fall within Enforcement Priority Category II should submit their Section 510(k), PMA, or PLA submissions as early as possible, in order to ensure that FDA will have sufficient time to complete its review before the 18 to 30 month time period elapses.

During this 18 to 30 month time period, manufacturers, importers, and distributors who have not obtained PMA or PLA approval or Section 510(k) clearance but claim exemption from the IDE regulations under 21 CFR 812.2(c) are to label their IVD's in accordance with 21 CFR 809.10(c). This regulation requires manufacturers, importers, and distributors to label their IVD's, as applicable: "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."

Additionally, in order to be in compliance with 21 CFR 809.10(c), manufacturers, importers, and distributors of uncleared and unapproved IVD's must remove any labeling statements that indicate that performance characteristics (e.g., sensitivity or specificity) or safety and effectiveness have been established for any indicated use. However, for three months from the publication date of the NOA for this CPG, the Agency does not intend to initiate enforcement action against manufacturers, importers, and distributors of IVD's in Enforcement Priority Category II who have failed to comply with these labeling requirements.

Appendix A provides guidance concerning definitions and labeling for research and investigational IVD's.

18 to 30 Month Period Not Applicable to New IVD's

The 18 to 30 month time period allotted for Enforcement Priority Category II devices to come into compliance through collection and submission of data does not apply to manufacturers, importers, and distributors of IVD's that were not in commercial distribution for diagnostic or prognostic purposes before the publication date of the NOA for this CPG. These products are required to have Agency clearance or approval, as appropriate, prior to commercialization and the Agency does not intend to exercise enforcement discretion with respect to these products.

"For Research Use Only" Devices Undergoing Laboratory Research

Devices marketed with labeling stating "For Research Use Only. Not for use in diagnostic procedures" that are not offered, sold, promoted, or used for diagnosis or prognosis in humans continue to be eligible for the exemption from the Investigational Device Exemptions regulation (21 CFR Part 812) if they comply with all applicable provisions of 21 CFR 812.2(c) and all labeling required by 21 CFR 809.10(c)(2)(I).

However, the Agency recognizes that many manufacturers, importers, and distributors have labeled their IVD's as "For Research Use Only" devices while allowing them to be investigated or commercialized for diagnosis or prognosis in humans. In order to fall within Enforcement Priority Category II, among other things, these mislabeled devices should be relabeled in accordance with 21 CFR 809.10(c)(2)(ii) to bear the statements: "For Investigational Use Only. The performance characteristics of this product have not been established." Note that investigational devices mislabeled as research devices will fall into Enforcement Priority Category I if not appropriately relabeled within three months of the publication date of the NOA for this CPG.

Applicability of IRB Approval and Informed Consent

Unless specifically exempted by the Protection of Human Subjects (21 CFR Part 50) or Institutional Review Board (IRB) (21 CFR Part 56) regulations, all sponsors of an investigational IVD exempted from the IDE regulation under the provisions of 21 CFR 812.2(c) are to obtain prior IRB approval of the study protocol and patient informed consent documents, and provide each patient with a copy of the informed consent document. See 21 U.S.C. 360j(g)(3).

Collection of Data

The data to be collected during the 18 to 30 month time period are to be based on scientifically sound controlled studies that are sufficient to 1) allow FDA to determine under a Section 510(k) submission that the device is substantially equivalent to a legally marketed predicate device, or 2) allow FDA to determine under a PMA application or PLA that the device is safe and effective for its labeled intended use(s). Additional guidance for data to be used in submissions to the Agency are discussed in Appendix B under "Collection of Data."

FDA strongly encourages investigational study sponsors to contact CDRH's Division of Clinical Laboratory Devices (DCLD) in the Office of Device Evaluation (ODE) or CBER's Office of Blood Research and Review to obtain guidance on appropriate study protocol design and data analysis techniques prior to initiation of the study.

Certification Programs

FDA encourages IVD manufacturers, importers, and distributors to develop certification programs that ensure proper research use or investigational use of IVD’s that have not yet received FDA approval or clearance, as appropriate, for commercial marketing. FDA believes that certification programs will help manufacturers, importers, and distributors of IVD’s ensure that the distribution and use of their IVD’s will be controlled and limited to use in scientifically sound research or investigations. A firm that has implemented a certification program is likely to be able to provide FDA with documentation to establish that a particular IVD labeled "For Research Use Only" or "For Investigational Use Only," in accordance with 21 CFR 809.10(c)(2)(I or ii), is not being commercialized for diagnostic or prognostic use.

The existence and use of a certification program does not relieve a manufacturer, importer, or distributor of any responsibilities under the Act or regulations, including the obligation to obtain Agency approval or clearance, as appropriate, for the device.

Guidance on appropriate elements for certification programs for IVD’s "For Investigational Use Only" and "For Research Use Only" is provided in Appendix C.

REGULATORY ACTION GUIDANCE:

Prior to initiation of regulatory action against observed violations, District Offices should evaluate any documentary evidence a firm may have to establish that the device is an appropriately labeled and used ASR or that there is limited distribution and use pursuant to laboratory research use, or alternatively, investigational use under a study protocol designed for collection of data to be submitted to FDA in a Section 510(k) notification, PMA application, or PLA.

If the IVD is subject to a PLA under the Public Health Service Act, appropriate charges, e.g., 42 U.S.C. 262, should be discussed with CBER's Office of Compliance (HFM-610).

If violations are identified, the District Office may prepare a Warning Letter to the firm. Concurrence from CDRH's or CBER's Office of Compliance is required before the letter is issued.

The charges listed below should be considered when a firm fails to comply with premarket notification or premarket approval requirements. These charges are immediately applicable to products that are in Enforcement Priority Category I. After the expiration of the 18 to 30 month time period, these charges may be used for products that are in Enforcement Priority Category II.

Examples of charges that may be applicable against violative products:

1. That the article is adulterated within the meaning of 21 U.S.C. 351(f)(1)(B), in that it is a Class III device under 21 U.S.C. 360c(f) and does not have an FDA approved premarket approval application in effect pursuant to 21 U.S.C. 360e or an approved application for an investigational device exemption under 21 U.S.C. 360j(g); and

2. That the article is misbranded within the meaning of 21 U.S.C. 352(o) in that a notice or other information respecting the device was not provided to the FDA as required by Section 510(k) and the device was not found by the Agency to be substantially equivalent to a device in interstate commerce prior to May 28, 1976 (the enactment date of the Medical Device Amendments).

If the firm fails to provide the District Office with adequate assurance that the IVD is an appropriately labeled and used ASR or that it is being used in an ongoing scientific study for collection of data or that deviations are being corrected, the District Office should consider appropriate enforcement action, including seizure, injunction, prosecution, and civil penalties.

## APPENDICES

Appendix A - Definitions and Labeling

I. IVD's That Are Intended for Investigational Use-Definitions

An "investigational device" is a device that is the object of an investigation (21 CFR 812.3(g)). "Investigation" means clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device (21 CFR 812.3(h)). Investigations of IVD's are necessary to determine the safety and effectiveness of the device for its intended clinical use, to develop performance characteristics for the product, and to establish the expected values. Unless exempt from premarket notification requirements, it is illegal to commercially market IVD's that have not been approved or cleared by FDA. Promotion and misrepresentation of an investigational device is prohibited by the Act and the Agency's regulations (21 U.S.C. 351(f)(1)(B) and 352(o), 21 CFR 812.7(a) and (d)).

II. Labeling "For Investigational Use" IVD's That Are Not Exempt under 21 CFR 812.2(c).

In accordance with 21 CFR 812.5, an investigational device or its immediate package shall bear a label with the following information:

1. The name and place of business of the manufacturer, packer, or distributor.

2. The quantity of contents, if appropriate, and the following statement:

   **"CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use."**

3. The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

4. An investigational device to be used for research on or with laboratory animals shall bear on its label the following statement:

   **"CAUTION - Device for investigational use in laboratory animals or other tests that do not involve human subjects."**

5. The labeling must not bear any statement that is false or misleading in any particular, not include any information on performance characteristics or reference ranges, and not represent that the device is safe or effective for the purposes for which it is being investigated.

III. Labeling "For Investigational Use Only" IVD's That Are Exempt under 21 CFR 812.2(c).

In accordance with 21 CFR 809.10(c), 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." This labeling is required even for those IVD's that fall within Enforcement Priority Category II and that FDA intends to allow manufacturers to continue to market for 18 to 30 months from the publication date of the NOA for this CPG.

IV. In Vitro Products Intended "For Research Use Only"

An in vitro product intended for research use is a product in the laboratory research phase of development. This research may use animal or human tissues. A research device cannot be intended for human clinical diagnostic or prognostic use. See 21 CFR 809.10(c)(2)(I).

Tests performed with in vitro products intended for research use are tests used in a preclinical or nonclinical setting. While research tests may be performed using either clinical or nonclinical materials, research use devices have no intended clinical use and the testing performed is not designed to provide data addressing or demonstrating safety and effectiveness. A clinical investigation intended to establish the safety and effectiveness of an IVD cannot be considered "research," even if only one human subject is involved.

The labeling requirements for a research in vitro product should include:

1. the name and place of business of the manufacturer, packer, or distributor as required by 21 CFR 801.1.

2. the statement "For Research Use Only. Not for use in diagnostic procedures," as required by 21 CFR 809.10(c)(2)(I).

Expected values (reference values) and specific performance characteristics described at 21 CFR 809.10(b)(11) and (12) should not be included in the labeling because one of the purposes of the research is to study and establish the subject IVD's performance parameters for its intended use.

FDA strongly encourages manufacturers, importers, and distributors of "research use" in vitro products to maintain a certification program that documents the researcher's agreement that the device will not be used for investigations involving clinical use including diagnosis, prognosis, and monitoring of a disease state and will not be used in conjunction with patient records or treatment.

V. Labeling, Marketing, and Advertising for Analyte Specific Reagents (ASR's)

In accordance with 21 CFR 809.10(e) an ASR shall bear labeling with the following information:

1. The proprietary name and established name (common or usual name), if any, of the reagent.

2. A declaration of the established name (common or usual name), if any.

3. The quantity, proportion, or concentration of the reagent ingredient; and for a reagent derived from biological material, the source and, where applicable, a measure of its activity. The quantity, proportion, concentration, or activity shall be stated in the system generally used and recognized by the intended user, e.g., metric, international units, etc.

4. A statement of the purity and quality of the reagent, including a quantitative declaration of any impurities present, and method of analysis or characterization. The requirement for this information may be met by a statement of conformity with a generally recognized and generally available standard that contains the same information, e.g., those established by the American Chemical Society, U.S. Pharmacopeia, National Formulary, and National Research Council. The labeling may also include information concerning chemical/molecular composition, nucleic acid sequence, binding affinity, cross-reactivities, and interaction with substances of known clinical significance.

5. A statement of warnings or precautions for users as established in the regulations contained in 16 CFR Part 1500 and any other warnings appropriate to the hazard presented by the product.

6. The date of manufacture and appropriate storage instructions adequate to protect the stability of the product. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, date of expiration, and other pertinent factors. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods, such as those described in 21 CFR 211.166.

7. A declaration of the net quantity of contents, expressed in terms of weight or volume, numerical count, or any combination of these or other terms that accurately reflect the contents of the package. The use of metric designations is encouraged, wherever appropriate.

8. The name and place of business of the manufacturer, packer, or distributor.

9. A lot or control number, identified as such, from which it is possible to determine the complete manufacturing history of the product.

10. For class I exempt ASR's, the statement: "Analyte Specific Reagent. Analytical and performance characteristics are not established."

11. For class II and III ASR's, the statement: "Analyte Specific Reagent. Except as a component of the approved/cleared test (name of approved/cleared test), analytical and performance characteristics of this ASR are not established."

12. In the case of immediate containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, and which are packaged within an outer container from which they are removed for use, the information required by paragraphs (e)(1) through (e)(6) of this section may appear in the outer container labeling only.

Analyte specific reagents may only be sold to:

1. In vitro diagnostic manufacturers;

2. Clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), as qualified to perform high complexity testing under 42 CFR Part 493, or clinical laboratories regulated under VHA Directive 1106 (available from the Department of Veterans Affairs, Veterans Health Administration, Washington, D.C. 20420); and

3. Organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners, e.g., forensic, academic, research, and other nonclinical laboratories (21 CFR 809.30(b)).

Advertising and promotional materials for analyte specific reagents:

1. Shall include the identity and purity (including source and method of acquisition) of the analyte specific reagent and the identity of the analyte;

2. Shall include the statement for class I exempt ASR's: "Analyte Specific Reagent. Analytical and performance characteristics are not established."

3. Shall include the statement for class II or III ASR's: "Analyte Specific Reagent. Except as a component of the approved/cleared test (name of approved/cleared test), analytical and performance characteristics are not established."; and

4. Shall not make any statement regarding analytical or clinical performance (21 CFR 809.30(d)).

Appendix B : Collection of Data

In order to obtain FDA approval or clearance, valid scientific data should be provided to the Agency in a Section 510(k) notification, PMA application, or PLA that supports all safety and effectiveness claims for the subject IVD. Manufacturers, importers, and distributors should have an appropriate plan or protocol in place in order to collect data to submit to FDA as part of a PMA application, PLA, or Section 510(k) notification. The study protocol and study data should be analyzed before and during the studies to ensure the validity of results. All premarket submissions should include information specifying and summarizing data that support the accuracy, precision, specificity, and sensitivity of the device. See 21 CFR 809.10(b)(12).

The FDA will notify firms whether their submissions have been approved or cleared. Firms are encouraged to include complete sets of data supporting safety and effectiveness in all submissions to the Agency. The Office of Device Evaluation has established a minimum threshold of acceptability for Section 510(k) submissions and will refuse to accept submissions where there are omissions of clearly necessary information. PMA submissions will also be refused for omissions of required information or inclusion of statements that are unsubstantiated by scientific evidence presented in the application.

The Division of Clinical Laboratory Devices (DCLD) has developed a series of guidance documents concerning IVD premarket submissions which may be obtained from CDRH's Division of Small Manufacturers Assistance (DSMA) or DCLD. Firms are encouraged to review these documents prior to sending in submissions to FDA, and to obtain comment and review from DCLD or CBER's Office of Blood Research and Review on proposed study protocols, data collection formatting, and data reporting for submissions to FDA.

Appendix C - Elements For Certification Programs

I. Certification Program for IVD's Intended and Labeled "For Investigational Use Only"

FDA strongly encourages manufacturers, importers, and distributors of IVD's intended and labeled "For Investigational Use Only" to develop certification programs. FDA believes certification programs are one way to demonstrate compliance with 21 CFR 812.2(c)(3).

FDA believes an effective certification program should include, but not necessarily be limited to, the following elements:

1. The manufacturer, importer, and distributor ensure that the subject IVD is distributed to and used by individuals, laboratories, or health care institutions who have provided written certification that they will comply with the investigational use of the device.

2. The manufacturer, importer, and distributor ensure that all written, printed, or graphic matter used to identify the subject IVD complies with the labeling requirements of 21 CFR 809.10(c)(2)(ii), which requires the labeling statement: "For Investigational Use Only. The performance characteristics of this product have not been established."

3. The manufacturer, importer, distributor, and end user maintain copies of signed certification documents, thereby creating an audit trail from the manufacturer to the end user. A simple certification procedure could involve a one-page document signed by the manufacturer, importer, distributor, and end user. Each person or business in the distribution chain attests, in the document, that the IVD will be used only for the purpose of gathering data to support appropriate submissions to the FDA, and will not be used for diagnostic purposes without confirmation by another medically established diagnostic device or procedure.

II. Certification Program for In Vitro Products Labeled "For Research Use Only"

FDA recommends that manufacturers, importers, distributors, and end users of in vitro products intended and labeled "For Research Use Only" who choose to implement a certification program include in the program, at minimum, the following elements:

1. Certification that the in vitro product is used for laboratory research and not used for a diagnostic or therapeutic purpose.

2. Certification that the research is not intended for determining the safety and effectiveness of the IVD.

by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA).

**FOR FURTHER INFORMATION CONTACT:** Margaret R. Schlosburg, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1223.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of September 26, 1997 (62 FR 50497), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under section 3507 of the PRA (44 U.S.C. 3507). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910–0352. The approval expires on November 30, 2000.

Dated: December 23, 1997.

**William K. Hubbard,**

*Associate Commissioner for Policy Coordination.*

[FR Doc. 98–075 Filed 1-2-98; 8:45 am]

**BILLING CODE 4160–01–F**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. 97D–0506]**

### Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only; Draft Compliance Policy Guide; Availability

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

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft Compliance Policy Guide (CPG) entitled ''Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only.'' The purpose of the CPG is to provide guidance on FDA's enforcement priorities concerning investigational or research IVD's that are being commercialized for diagnostic or prognostic purposes.

**DATES:** Written comments on the draft CPG may be submitted by April 6, 1998.

**ADDRESSES:** Submit written comments on the draft CPG to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written requests for single copies of the draft CPG to the Division of Small Manufacturers Assistance (DSMA), Center for Devices and Radiological Health (CDRH) (HFZ–220), Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850 (301–443–6597 or outside MD 1–800–638–2041). Send two self-addressed adhesive labels to assist that office in processing your requests, or FAX your request to 301–443–8818. Facsimiles of the draft CPG are available from the Division of Small Manufacturers Assistance, CDRH. To receive the draft CPG on your fax machine, call the CDRH Facts-On-Demand system at 1–800–899–0381 or 301–827–0111 from a touch tone telephone. At the first voice prompt press ''1'' to access DSMA Facts, at the second voice prompt press ''2,'' and then enter the document number, ''671,'' followed by the pound sign, ''#''. Follow the remaining voice prompts to complete the request. Copies of the draft CPG may also be downloaded to a personal computer with access to the World Wide Web (www). The Office of Regulatory Affairs (ORA) and CDRH Home Pages include the draft CPG and may be accessed at ''http://www.fda.gov/ora'' or ''http://www.fda.gov/cdrh'' respectively. The draft CPG will be available on the Compliance References or Compliance Information pages for ORA and CDRH respectively.

**FOR FURTHER INFORMATION CONTACT:** Betty W. Collins, Office of Compliance (HFZ–300), Center for Devices and Radiological Health, Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301–594–4588, ext. 165.

**SUPPLEMENTARY INFORMATION:** FDA has developed a draft CPG to provide guidance on FDA's enforcement priorities concerning investigational or research IVD's that are being commercialized for diagnostic or prognostic purposes. This draft CPG applies to IVD's sold or distributed as test kits. Many manufacturers of IVD's have not followed the requirements set forth in parts 809 and 812 (21 CFR parts 809 and 812). As a result, numerous IVD's labeled for research or investigational purposes are being promoted, distributed, and used for commercial purposes. This has resulted in the widespread use of laboratory tests with unproven performance characteristics. Unless exempted from the requirement to submit premarket notification under section 510(k) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b(k)), IVD's that are commercially distributed for diagnostic use prior to FDA approval or clearance are adulterated and misbranded under sections 501(f)(1)(B) and 502(o) of the act (21 U.S.C. 351(f)(1)(B) and 352(o)). Such distribution subjects the devices and responsible firms to regulatory action.

However, FDA recognizes that certain improperly commercialized IVD's have been in extensive clinical use for a significant period of time. FDA further recognizes that immediate regulatory action against certain IVD's might result in adverse consequences to individual patients and the public health. Therefore, FDA has prepared a draft CPG in order to describe its enforcement policy. Except in specified instances, FDA does not intend to initiate enforcement action, for 18 to 30 months from the **Federal Register** publication date of the notice of availability (NOA) for the final CPG on commercialization of IVD's labeled for research use only or investigational use only, against IVD's that have not been approved or cleared, provided the IVD manufacturers, importers, and distributors take steps and obtain FDA approval of a premarket approval application, product license application, or clearance of a premarket notification submission under section (510(k)) of the act during that time period. Those steps include undertaking, by 6 months from the **Federal Register** publication date of the NOA for the final CPG, any necessary clinical investigations or other studies under a protocol sufficient to allow determination of the IVD's safety and effectiveness. FDA believes that the 18- to 30-month time period is a reasonable period for gathering safety and effectiveness data and obtaining FDA approval or clearance. This draft CPG applies to IVD's that are regulated by FDA's CDRH and Center for Biologics Evaluation and Research, and supersedes FDA's earlier draft made public in June 1996.

This draft CPG does not cover analyte specific reagents (ASR's) that, as specified under §§ 809.10(e), 809.30, and 864.4020 (21 CFR 864.4020), are not labeled or promoted with performance claims, and are sold to: (1) In vitro diagnostic manufacturers; (2) clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 as qualified to perform high complexity testing under 42 CFR part 493 or clinical laboratories regulated under the Veterans Health Administration Directive 1106; and (3) organizations that use the ASR to make tests for purposes other than providing diagnostic information to patients and practitioners. ASR's are defined as

antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens. FDA's final rule on ASR's was published in the **Federal Register** of November 21, 1997 (62 FR 62243).

Additionally, this draft CPG does not pertain to in vitro products whose use is limited to laboratory research that is entirely unrelated to the development of IVD's.

This draft guidance document represents the agency's current thinking on commercialization of in vitro diagnostic devices labeled for research use only or investigational use only. 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.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the draft CPG entitled ''Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only.'' Two copies of any comments are to be submitted, 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. The agency will review all comments, but in issuing a final CPG, need not specifically address every comment. The agency will make changes to the CPG in response to comments, as appropriate. A copy of the draft CPG and received comments may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: December 22, 1997.

**Gary Dykstra,**

*Acting Associate Commissioner for Regulatory Affairs.*

[FR Doc. 98–011 Filed 1-2-98; 8:45 am]

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. 97D–0525]**

### Draft Guidance for Industry: ''Promoting Medical Products in a Changing Healthcare Environment; I. Medical Product Promotion by Healthcare Organizations or Pharmacy Benefits Management Companies (PBMs)''

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

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled ''Promoting Medical Products in a Changing Healthcare Environment; I. Medical Product Promotion by Healthcare Organizations or Pharmacy Benefits Management Companies (PBMs).'' This document provides guidance to sponsors of regulated medical products (human drugs, biologics, and medical devices) by describing circumstances in which sponsors may be held responsible for promotional activities performed by healthcare organizations or PBM's that violate the Federal Food, Drug, and Cosmetic Act (the act) and regulations issued thereunder. The intent of this draft guidance is to provide clarification and consistency in the agency's regulation of medical product promotion in light of changes in the healthcare environment.

**DATES:** Written comments may be submitted on the draft guidance document by April 6, 1998. General comments on agency guidance documents are welcome at any time.

**ADDRESSES:** An electronic version of this draft guidance is available on the Internet using the World Wide Web (WWW) at http://www.fda.gov/cder/guidance.htm. Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm 1–23, Rockville, MD 20857. Submit written requests for single copies of the draft guidance for industry entitled ''Promoting Medical Products in a Changing Healthcare Environment; I. Medical Product Promotion by Healthcare Organizations or Pharmacy Benefits Management Companies (PBMs)'' to the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your request. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the draft guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

**FOR FURTHER INFORMATION CONTACT:**

Regarding prescription drugs: Laurie B. Burke, Center for Drug Evaluation and Research (HFD–40), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2828, or via Internet at burkel@cder.fda.gov;

Regarding prescription biological products: Toni M. Stifano, Center for Biologics Evaluation and Research (HFM–200), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–3028, or via Internet at stifano@cber.fda.gov;

Regarding restricted medical devices: Byron L. Tart, Center for Devices and Radiological Health (HFZ–302), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301–594–4639, or via Internet at bxt@cdrh.fda.gov.

**SUPPLEMENTARY INFORMATION:**

#### I. Background

*A. FDA's Guidance Document Development Process*

On March 28, 1997, as part of the agency's ongoing efforts to ensure meaningful public participation in the guidance document development process, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) requested public comment on guidance documents relating to prescription drug advertising and labeling (Ref. 1). Included in the list of currently proposed guidance documents was ''Promotion to Managed Care Organizations.'' The draft guidance document now being made available is the first draft document to be issued on this topic and addresses only one aspect of promotion to managed care, i.e., promotion by healthcare organizations or PBM's. Other related draft guidance documents will be issued separately under the general heading ''Promoting Medical Products in a Changing Healthcare Environment.''

*B. Statutory and Regulatory Requirements*

Under the act, FDA has responsibility for regulating the labeling and, in many cases, the advertising of medical