Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only

Guidance for Industry and Food and Drug Administration Staff

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For questions regarding this document contact Elizabeth Mansfield, by phone at (301) 796-4664, or by email at elizabeth.mansfield@fda.hhs.gov. For questions relating to devices regulated by CBER, contact the Office of Communications, Outreach and Development, CBER at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety

Center for Biologics Evaluation and Research

Preface

Public Comment

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Office of Communication, Outreach and Development, HFM-40

Center for Biologics Evaluation and Research

Food and Drug Administration

1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448

Internet: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

Tel: 800-835-4709 or 301-827-1800

E-mail: ocod@fda.hhs.gov

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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.

I. Introduction

FDA is issuing this guidance document to provide the current thinking of the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) on when in vitro diagnostic (IVD) products[1] are properly labeled "for research use only" (RUO) or "for investigational use only" (IUO)[2]. FDA is concerned that the distribution of unapproved and uncleared IVD products labeled RUO or IUO, but intended for purposes other than research or investigation (for example, for clinical diagnostic use[3]), has led, in some cases, to the clinical diagnostic use of products with unproven performance characteristics, and with manufacturing controls that are

[1] "*In vitro diagnostic products* are those 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. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act." Title 21, Code of Federal Regulations (CFR), section 809.3(a).

[2] This guidance is only intended to apply to IVD products that have not been approved, cleared or licensed for any use, and it is not intended to address off-label uses of any approved, cleared or licensed products.

[3] Throughout this guidance document, references to "clinical diagnostic use" and "use in clinical diagnosis" include use in making medical treatment decisions.

inadequate to ensure consistent manufacturing of the finished product. Use of such tests for clinical diagnostic purposes may mislead healthcare providers and cause serious adverse health consequences to patients, who are not aware that they are being diagnosed with or treated based on the results of tests with research or investigational products. FDA is issuing this guidance to clarify the requirements applicable to RUO and IUO IVD products, including that RUO and IUO labeling must be consistent with the manufacturer's intended use of the device.

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.

II. Regulatory Requirements for Research Use Only and Investigational Use Only IVD products

Section 520(g) of the FD&C Act, 21 U.S.C. 360j(g), provides for the exemption of devices intended for investigational use from certain requirements of the Act if such devices comply with the procedures and conditions prescribed by that section and by regulation. For example, devices intended for investigational use that meet applicable requirements may be exempted from premarket notification and premarket approval requirements of sections 510, 515, 520(g)(2)(A) of the Act (21 U.S.C. 360, 360e, 21 U.S.C. 360j(g)(2)(A)); *see also* 21 CFR 812.1(a). A product's intended use refers to the "objective intent" of those responsible for labeling the product.[4] Intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article.[5]

Device Investigations Subject to IDE Regulation
FDA's investigational device exemption (IDE) regulation is found at 21 CFR part 812. Under 21 CFR 812.5, investigational devices must bear a label that states the following: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use." The labeling may not represent that the device is safe or effective for the purposes for which it is being investigated. 21 CFR 812.5(b). The IDE regulation also prohibits certain conduct by sponsors and investigators pertaining to the investigation and distribution of investigational devices, among other practices. See 21 CFR 812.7.

Device Investigations Exempt from IDE Regulation
Investigations of diagnostic devices that meet the criteria at section 812.2(c)(3) are exempt from the regulations at 21 CFR 812, with the exception of section 812.119. The criteria at section 812.2(c)(3) include specifying that testing:

[4] See, 21 CFR 801.4
[5] See, id.

- be non-invasive,
- not require an invasive sampling procedure that presents a significant risk,
- not by design or intention introduce energy into a subject, and
- not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

The criteria in section 812.2(c)(3) also include compliance with labeling requirements section CFR 809.10(c), which exempts shipments and other deliveries of IVDs from certain labeling requirements if either (1) the device complies with part 812, or (2) the investigation is not subject to part 812 and one of the following conditions is met:

(i) For a product in the laboratory research phase of development, and not represented as an effective in vitro diagnostic product, all labeling bears the statement, prominently placed: "For Research Use Only. Not for use in diagnostic procedures."

(ii) For a product being shipped or delivered for product testing prior to full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful), all labeling bears the statement, prominently placed: "For Investigational Use Only. The performance characteristics of this product have not been established."

For purposes of this guidance document, "labeled RUO" refers to IVD products labeled in accordance with section 809.10(c)(2)(i); "labeled IUO" refers to IVD products labeled in accordance with section 809.10(c)(2)(ii) unless otherwise specified. Examples of products that meet the criteria for these designations are provided in Section III.

Because these products are exempt from most regulatory controls, it is important that they are not distributed for clinical diagnostic uses.

Mere placement of an RUO or IUO label on an IVD product does not render the device exempt from otherwise applicable clearance, approval, or other requirements. FDA may determine that the device is intended for use in clinical diagnosis based on other evidence, including how the device is marketed.

In general, if evidence shows that an IVD product is inappropriately labeled RUO or IUO, and that the product does not qualify for an investigational device exemption under 520(g) of the Act, and is not cleared, approved, or 510(k)-exempt, the device would be misbranded under sections 502(a) and 502(o) of the Act, 21 U.S.C. 352(a), 352(o), and adulterated under section 501(f) of the Act, 21 U.S.C. 351(f).

III. Research Use Only and Investigational Use Only In Vitro Diagnostic Products

Both RUO and IUO products are IVD products currently under development and not approved for clinical diagnostic use. Because they are being shipped for investigations pertaining to product development and not clinical use, these products are exempt from most regulatory controls including IDE regulation. The term RUO refers to devices that are in the laboratory phase of development. The term IUO refers to devices that are in the product testing phase of development.

A. Research Use Only In Vitro Diagnostic Products

An RUO product is an IVD product that is in the laboratory research phase of development and is being shipped or delivered for an investigation that is not subject to part 812. During the research phase of development, the focus of manufacturer-initiated studies is typically to evaluate design, limited-scale performance, and issues such as usability of the test. Some examples of products FDA would consider to be in this research phase include:

- Tests that are in development to identify test kit methodology, necessary components, and analytes to be measured.
- Instrumentation, software, or other electrical/mechanical components under development to determine correct settings, subcomponents, subassemblies, basic operational characteristics, and possible use methods.
- Reagents under development to determine production methods, purification levels, packaging needs, shelf life, storage conditions, etc.

FDA also recognizes that there are certain products, such as instruments, systems, and reagents that are labeled for research use only and intended for use in the conduct of non-clinical laboratory research with goals other than the development of a commercial IVD product, i.e., these products are used to carry out research and are not themselves the object of the research. These include products intended for use in discovering and developing medical knowledge related to human disease and conditions. For example, instruments and reagents intended for use in research attempting to isolate a gene linked with a particular disease may be labeled for research use only when such instruments and reagents are not intended to produce results for clinical use.

B. Investigational Use Only In Vitro Diagnostic Products

An IUO product is an IVD product that is being shipped or delivered for product testing that is not subject to 21 CFR part 812 (with the exception of §812.119, Disqualification of clinical investigator) prior to full commercial marketing (for example, for testing of specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful). Examples of IVD products under investigation that FDA considers to fall in this category include those that are being

evaluated in comparison studies that use archived or fresh specimens to determine performance characteristics.

IV. Appropriate Labeling and Distribution Practices for RUO and IUO Products

A. Labeling of RUO and IUO IVD Products

1. Research Use Only Labeling

With respect to IVD products that are appropriately labeled RUO, the RUO labeling is meant to serve as a warning, to prevent such products from being used in clinical diagnosis, patient management, or an investigation that is not exempt from 21 CFR part 812. In general, IVD products that are intended for clinical diagnosis or patient management must be labeled "For *In vitro* diagnostic use"[6] and be in compliance with all relevant regulations for *In vitro* diagnostic devices.

An IVD product should not be labeled RUO if it is intended for use in a clinical investigation subject to 21 CFR part 812 or for clinical diagnostic use outside an investigation (for example, in clinical diagnosis for standard medical practice). FDA would consider such an IVD product to be misbranded under section 502(a) of the Act, 21 U.S.C. 352(a), if it were labeled "For Research Use Only" or otherwise labeled solely for research use, because such labeling would be false or misleading.

2. Investigational Use Only Labeling

Similarly, with respect to IVD products that are appropriately labeled IUO, the IUO labeling is meant to serve as a warning that products so labeled should not be used in clinical diagnosis, patient management, or an investigation that is not exempt from 21 CFR part 812.

An IVD product should not be labeled IUO if it is intended for non-investigational purposes, such as in clinical diagnostic use outside of an investigation. FDA would consider such an IVD product to be misbranded under section 502(a) of the Act, 21 U.S.C. 352(a), if it was labeled with the statement: "For Investigational Use Only" or "Investigational device."[7]

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[6] 21 CFR 809.10(a)(4). Alternatively, some IVD products may be appropriately labeled as analyte specific reagents (see 21 CFR 864.4020 and 21 CFR 809.10(e)(1)(x) or (xi), or as general purpose reagents (see 21 CFR 864.4010 and 21 CFR 809.10(d)(1)(iv)).

[7] IVD products intended for investigational use in a manner that is not consistent with an exempted investigation (see 21 CFR 812.2(c) for a description of exempted investigations) must comply with the Investigational Device Exemption (IDE) requirements in 21 CFR part 812 in order to be exempt from many requirements otherwise applicable to medical devices. Instead of being labeled IUO, they must be labeled

B. Distribution Practices that are Inconsistent with RUO/IUO Designations

A product's intended use refers to the "objective intent" of those legally responsible for labeling the product[8], which may be determined by looking at the totality of circumstances surrounding the distribution of the article.[9] Overt expressions by the manufacturer, such as those present in labeling and advertising, may be sufficient to show determine that an IVD product is in appropriately labeled RUO or IUO, when such expressions demonstrate that the device is actually intended for clinical use despite the RUO or IUO labeling. Other evidence of the intended use of a product could include the design of the product, other statements by the manufacturer about the device, and how the device is sold and distributed by or on behalf of the manufacturer. The following are examples of evidence of intended uses that, depending on the totality of the circumstances surrounding the distribution of the article, would appear to conflict with RUO or IUO labeling:

- Written or verbal statements in any labeling, advertising, or promotion of the IVD product by or on behalf of the manufacturer, including any performance claims, instructions for clinical interpretation, clinical information, product names, or descriptors that claim or suggest that the IVD product may be used for any clinical diagnostic use, including a clinical investigation subject to part 812. This may include workshops or presentations that describe clinical uses of products labeled RUO or IUO that do not include appropriate statements and warnings about the research or investigational nature of the products;
- Written or verbal statements in any labeling, advertising, or promotion of the IVD product by or on behalf of the manufacturer that suggest that clinical laboratories can validate the test through their own procedures and subsequently offer it for clinical diagnostic use as a laboratory developed test.
    - Solicitation of business from clinical laboratories; for example, a manufacturer who produces only products labeled RUO whose sales force makes routine calls to clinical laboratories that do not perform research or clinical studies may be viewed as demonstrating its intent that its products be used for clinical purposes.
- Provision of certain types of specialized technical support [10] (e.g., assistance in performing clinical validation) to clinical laboratories.

"CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use." 21 CFR 812.5.

[8] For the purposes of this guidance document, the term "manufacturer" 21 CFR 806.2(g) is taken as synonymous with "persons legally responsible for the labeling of devices" 21 CFR 801.4. The term "manufacturer" is used as a convenience throughout the guidance.

[9] See 21 CFR 801.4.

[10] Note: FDA is not referring here to generic maintenance support or software updates for an RUO or IUO IVD product.

Other practices, though not themselves in conflict with RUO or IUO labeling, may support a finding of a conflicting intended use when accompanied by behavior described above. For example, when there is a past history of distribution of a product intended for clinical diagnostic use as an analyte specific reagent (ASR), and the product is now labeled as RUO or IUO, without any change in distribution practices such as advertising to and solicitation of business from clinical laboratories, the "new" RUO/IUO labeling is likely to be inconsistent with the intended use of the manufacturer.

Other practices may or may not indicate an intended use that is consistent with RUO/IUO labeling, depending on the context. For example:

1. Instructions for use for an IVD product labeled RUO or IUO

FDA may consider all labeling for the product, including the content of the instructions for use and descriptive language in package inserts provided with the product as evidence of intended use.

In certain circumstances, such as when the use of an IVD product labeled for research use only is limited to use in the conduct of laboratory research that is unrelated to the development of IVDs, providing instructions for correctly using the product in a research manner (for example, mixing proportions, incubation times, storage conditions, etc.) would be considered to be consistent with research use only labeling. However, inclusion of clinical interpretive information, discussion of clinical significance, or other indications of clinical applicability included with any IVD products labeled for research use only would suggest that such products are not intended for research use only, but rather that they are intended for non-research clinical diagnostic purposes. FDA would consider the provision of such information as evidence of an intended use that would appear to conflict with research use only labeling, and requires compliance with all applicable device requirements under the FD&C Act.

FDA believes that those products that are being distributed for use in the research phase of IVD development may be unlikely to need instructions for use, as such products are still in their formative stages, and provision of instructions for using such products may not always be necessary. If basic instructions for use are needed in order to properly configure or use the device in the research phase of development, provision of these may be viewed as consistent with RUO labeling. For IVD products labeled IUO that are the subject of a clinical investigation by a sponsor other than the manufacturer, it is acceptable (and perhaps necessary) for the manufacturer to provide instructions for use to the sponsor of the study using the format described in 21 CFR 809.10(b).

2. Validation and verification of clinical diagnostic testing using IVD products labeled RUO or IUO

FDA views the activities of a manufacturer that aid the clinical laboratory in validation

or verification of a test that incorporates RUO or IUO labeled IVD products as evidence of the manufacturer's intended use. If the manufacturer of an IVD product labeled RUO or IUO were to assist in the validation or verification of the performance of a test for clinical diagnostic use that uses its RUO or IUO labeled IVD, that assistance would be considered to be evidence of a non-research or non-investigational intended use. FDA would consider such evidence along with the totality of the circumstances.

In contrast, the manufacturer of an appropriately labeled RUO or IUO device may provide support services such as general repair or maintenance, and general non-diagnostic use-specific technical support, because, in general, these would not constitute evidence of a non-research or non-investigational intended use.

FDA recommends that manufacturers assess the totality of the circumstances surrounding the sale and distribution of their RUO and IUO labeled IVD products to ensure that they are not engaging in practices that conflict with their labeling.

C. Other Relevant Practices

1. Use of a "certification program"

The totality of the circumstances surrounding the distribution and use of an RUO or IUO product should be considered when assessing its intended use. User certification programs, where users certify that they will not use RUO/IUO products in a manner inconsistent with the labeling, would be viewed as one factor to consider when assessing these circumstances. However, the existence of a certification program alone would not relieve manufacturers from their responsibilities to ensure that their labeling and distribution practices for RUO/IUO products are consistent with the product's RUO/IUO label.

2. Software labeled RUO or IUO

Software that is a stand-alone IVD product, or a component of or an accessory to another IVD product, which is labeled for research or investigational use only, may be distributed for research or investigational use to entities conducting research or investigations with the software.

V. FDA's Compliance Approach

Manufacturers must comply with all applicable requirements under the FD&C Act and FDA regulations for those IVD products that are intended for use in clinical diagnostic applications. For devices that are not used in research or investigation, these requirements generally include registration of the manufacturer and listing of the device(s), compliance with current Good Manufacturing Practices, and reporting of adverse events, among other general controls. There are also specific requirements for various device types, for example,

analyte specific reagents. *See* 21 CFR 809.10(e), 809.30, & 864.4020. While some IVD products, including some analyte specific reagents, are exempt from premarket notification, other products require premarket clearance or approval. Where the appropriate regulatory pathway is unclear, manufacturers are encouraged to discuss the matter with FDA.

When determining whether non-compliance with statutory and regulatory requirements warrant a regulatory and/or enforcement action, FDA intends to consider the totality of the circumstances concerning a manufacturer's sale and distribution of a product labeled as RUO or IUO.

In general, if evidence shows that an IVD product is inappropriately labeled RUO or IUO, and that the product does not qualify for an investigational device exemption under 520(g) of the Act, and is not cleared, approved, or 510(k)-exempt, the device would be misbranded under sections 502(a) and 502(o) of the Act, 21 U.S.C. 352(a), 352(o), and adulterated under section 501(f) of the Act, 21 U.S.C. 351(f).