Draft Guidance for Industry and Food and Drug Administration Staff

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Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational

Preface

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Draft Guidance for Industry and Food and Drug Administration Staff

Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions

This draft guidance when finalized will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 pagi

This document is intended for manufacturers and distributors of RUO and IUO IVD products and any other entities who label IVD products.[3]

RUO and IUO IVD products are distinctive in that they are devices that may themselves be used in research or investigations on human samples that may eventually lead to their clearance or approval for clinical diagnostic use,[4] and they also may be marketed for and used in the research and investigation of other FDA-regulated products. Thus, the manufacturer of an IUO IVD product is not necessarily the sponsor of a clinical investigation that uses such an IVD product in a study. The manufacturer of such an IUO IVD product may legally distribute the product commercially without FDA premarket review, as long as the distribution is only for investigational use.

The marketing of unapproved and uncleared IVD products for purposes other than research or investigation (for example, for clinical diagnostic use) has led in some cases to diagnostic use of laboratory tests with unproven performance characteristics and manufacturing controls that are 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 research or investigational products. FDA is therefore issuing this guidance to remind manufacturers of the requirements applicable to RUO and IUO IVDs.

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.

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. 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 practices by sponsors and investigators pertaining to the marketing and distribution of investigational devices. 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 21 CFR 812, with the exception of section 812.119. The criteria at section 812.2(c)(3) include compliance with section 809.10(c) and specify that testing:

- 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.

Labeling requirements regarding IVD products are found at 21 CFR part 809. Pursuant to 21 CFR 809.10(c), shipments and other deliveries of IVDs are exempt from the IVD labeling requirements at section 809.10(a) and (b) if either (1) there has been compliance 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

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.

Although IVD products intended solely for research use are generally exempt from most regulatory requirements, 21 CFR 807.65 does not specifically exempt foreign manufacturers who import RUO IVD products into the U.S. from establishment registration and device listing requirements. At this time, FDA intends to exercise enforcement discretion with respect to establishment registration and device listing requirements for persons who manufacture, propagate, compound, or process imported IVD products intended solely for research use. The following product codes for required importation documents reflect RUO IVD uses.

IVD Panel	**Product Code**
Hematology RUO IVD products	OTQ
Clinical Chemistry RUO IVD products	OTV
Clinical Toxicology RUO IVD products	OTW
Pathology RUO IVD products	OTU
Microbiology RUO IVD products	OTT
Immunology RUO IVD products	OTR

Manufacturers of devices regulated by CBER should contact CBER to discuss product identifiers for RUO IVDs for use on required importation documents.

III. Frequently Asked Questions

A. Research Use Only and Investigational Use Only IVD products

1. What types of products does FDA generally consider to be appropriately labeled

components, and analytes to be measured;

- Instrumentation 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 and storage life, etc.

FDA also recognizes within the category of RUO IVD products certain products intended for use in non-clinical laboratory research with goals other than the development of a commercial IVD product. These include products intended for use in discovering and developing novel and fundamental 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 RUO when such instruments and reagents are not intended to produce results for clinical use.

With respect to both categories of RUO IVD products, the required labeling is meant to serve as a warning that products so labeled should not be used in clinical diagnosis or patient management.

2. What types of IVD products should not be labeled RUO?

Any IVD product that is intended for use in a c

under investigation that FDA would consider to fall in this category include those that are being evaluated in comparison studies that us

2. What marketing practices would FDA consider to be generally inappropriate for

FDA will assess the following marketing practices as evidence of an intended use that conflicts with IUO labeling, and is thus generally inappropriate for IVD products labeled IUO:

- Written or verbal statements in any labeling, advertising, or promotion of the IVD product that claim or suggest that the IVD product may be used in non-investigational clinical diagnostic use;
- Written or verbal statements in any labeling, advertising, or promotion of the IVD product that claim or suggest that the IVD product may be used in a manner that is inconsistent with an exempt investigation (see 21 CFR 812.2(c));
- Sales to clinical laboratories that the manufacturer knows, or has reason to know, use the IVD product in non-investigational clinical diagnostic use or in an investigation that is not exempt from 21 CFR part 812 and support (including technical support) for those activities.
- Past history of promotion of the product

3. What should a manufacturer do if it learns that one of its clinical laboratory[7] customers wants to use an IVD product labeled RUO or IUO in clinical diagnosis?

FDA is aware that laboratories sometimes use IVD products labeled RUO in clinical diagnosis and that many manufacturers, importers, and distributors of IVD products labeled RUO are also aware of such use. Manufacturers who label their IVD products: "For Research Use Only. Not for use in diagnostic procedures," should not sell such products to laboratories that they know use the product for clinical diagnostic use. If a manufacturer learns that a laboratory to which it sells its RUO-labeled IVD product is

Manufacturers who label their IVD products IUO should not sell them to laboratories that they know use the product for clinical diagnostic use outside of a clinical investigation. If a manufacturer learns that a clinical laboratory to which it sells its IUO-labeled IVD product is using these IUO-labeled IVDs for non-investigational diagnostic use, it should halt sales for such use or comply with FDA regulations for IVD products, including premarket review requirements, if applicable.

4. Can a manufacturer obtain clearance or approval for an IVD product that includes or is required to be used with one or more IUO and/or RUO-labeled reagents or instruments?

A manufacturer that is planning to submit a premarket notification (510(k)), an application for premarket approval (PMA), or a biologics license application (BLA) for a test that uses an RUO or IUO-labeled reagent or instrument should include data regarding the RUO or IUO product as part of their submission. Once the IVD product is cleared or approved, the RUO or IUO-labeled reagent and/or instrument should be relabeled to indicate that it is cleared or approved for use with that specific IVD product.

5. Should a manufacturer or distributor promote IVD components, instruments, or reagents labeled RUO or IUO for use in an LDT that the manufacturer knows is used in clinical diagnosis?

No. Labeling an IVD component, instrument, or reagent RUO or IUO is not consistent with their use in an LDT used in clinical diagnosis. FDA would consider promotion of IVD components, instruments, or reagents labeled RUO or IUO for use in an LDT that the manufacturer knows is used to provide clinical results outside an investigation to be evidence of an intended use that conflicts with RUO and IUO labeling, which may render the device misbranded under section 502(a) of the Act, 21 U.S.C. 352(a). As explained in section III.B.2. above, unless exempt from premarket notification requirements, if such an IVD product were not cleared or approved, it may also be rendered adulterated under section 501(f) of the Act, 21 U.S.C. 351(f) and misbranded under section 502(o) of the Act, 21 U.S.C. 352(o).

6. Should the manufacturer include instructions for use with an IVD product labeled RUO or IUO?

In certain circumstances, such as when the use of an IVD product labeled RUO is limited to laboratory research that is unrelated to the development of IVDs (see discussion in section III.A.1. above), general instructions for using the product (for example, mixing proportions, incubation times, etc.) may be provided. However, no clinical interpretive information, discussion of clinical significance, or other indications of clinical applicability should be included with any IVD products labeled RUO, as this would suggest that they may be used for non-research purposes, which would conflict with their RUO labeling. For those products that are in the research phase of IVD development,

there is unlikely to be a need for instructions for use, as such products are still in their formative stages.

For IVD products labeled IUO that are the subject of a clinical investigation by a sponsor other than the manufacturer, it is acceptable to provide instructions for use to the sponsor of the study using the format described in 21 CFR 809.10(b).

7. Is it appropriate for a manufacturer or distributor to market software labeled RUO or IUO?

Yes, software that is a stand-alone IVD product, or a component of or an accessory to another IVD product, which is labeled in accordance with 21 CFR 809.10(c)(2), may be marketed for research or investigational use to entities conducting research or investigations with the software. Such software is subject to the same limitations on promotion and marketing as other IVD products labeled RUO or IUO.

8. Should the manufacturer of an IVD product labeled RUO or IUO help with the validation and verification of performance specifications of an LDT or other test that the manufacturer knows is used in clinical diagnosis that utilizes its product?

No. If the manufacturer of an IVD product labeled RUO were to assist in the validation or verification of the performance of a test that the manufacturer knows is used in clinical diagnosis using its RUO-labeled IVD product, FDA would consider such assistance to be evidence of non-research intended use. As explained above, this may render the device 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).

If the manufacturer of an IVD product labele