Draft Guidance for Industry and FDA Staff - Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Q...

U.S. Food & Drug Administration

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For questions regarding this document contact Tonya Wilbon at 301-796-6224 (tonya.wilbon@fda.hhs.gov [1]). For questions regarding this document as applied to devices regulated by CBER contact the Office of Communication, Outreach and Development (OCOD), 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov [2].

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 Biologic Evaluation and Research

Preface

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This draft guidance when finalized will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

A. Research Use Only and Investigational Use Only IVD products

1. What types of products does FDA generally consider to be appropriately labeled "Research Use Only" IVD products?

As explained above, 21 CFR 809.10(c)(2)(i) exempts IVD products intended only for research use from the IVD labeling requirements at section 809.10(a) and (b) if the product is in the laboratory research phase of development, is not represented as an effective in vitro diagnostic product, and is labeled: “For research use only. Not for use in diagnostic procedures.”

During the laboratory 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 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 clinical investigation or clinical diagnostic use outside an investigation (for example, in clinical diagnosis) should not be labeled RUO. 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 RUO or otherwise labeled for research use.

3. What types of products does FDA generally consider to be appropriately labeled "Investigational Use Only" IVD products?

Investigational IVD products are those that are the subject of an investigation. 21 CFR 812.3(g). As explained above, investigational IVD products may or may not be subject to most provisions of 21 CFR 812. Investigational IVD products that do not meet the exemption criteria of section 812.2(c)(3) must comply with part 812, including the requirement that they bear a label with the statement: "CAUTION--Investigational device. Limited by Federal law to investigational use." 21 CFR 812.5.

In order to be exempt from 21 CFR 812, an investigation of an IVD product must meet the criteria of section 812.2(c)(3) (see above), including that it not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically-established diagnostic product or procedure. If the investigation meets these

criteria, a product being shipped or delivered for product testing prior to full commercial marketing is exempt from the IVD labeling requirements at section 809.10(a) and (b) as long as it is labeled: "For Investigational Use Only. The performance characteristics of this product have not been established.” 21 CFR 809.10(c)(2)(ii). For example, IVD products under investigation that FDA would consider to fall in this category include those that are being evaluated in comparison studies that use archived or fresh specimens to determine performance characteristics.

4. What types of IVD products should not be labeled IUO?

Any IVD product that is intended for non-investigational purposes, such as in clinical diagnostic use outside of an investigation, should not be labeled IUO. 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 is labeled with the statement: "For Investigational Use Only" or “Investigational device.”
Investigational IVD products subject to 21 CFR 812 must be labeled in accordance with section 812.5 and should not be labeled in accordance with section 809.10(c)(2)(ii). Investigational IVD products exempt from part 812 under section 812.2(c)(3) must be labeled in accordance with section 809.10(c)(2)(ii) and should not be labeled in accordance with section 812.5.

5. Are RUO and IUO IVD products required to be manufactured in compliance with the Quality System regulation?

FDA does not require RUO IVD products or IUO IVD products that meet the conditions for exemption from 21 CFR 812 to be manufactured in compliance with the Quality System (QS) regulation (21 CFR 820). Investigational use IVD products that are not exempt from 21 CFR 812 and that comply with part 812 are exempt from QS requirements except for those found in 21 CFR 820.30 (design controls), if applicable. 21 CFR 812.1(a). Thus, investigational use IVD products that are not exempt from part 812 should not be shipped to sites for investigational use until required design control activities have been completed and documented, as required by section 820.30, if applicable.

B. Marketing Practices of Manufacturers who Label their IVD Products RUO and IUO

1. How may IVD products labeled RUO or IUO be marketed?

As explained above, RUO and IUO IVD products may be studied for clearance or approval, but they also may be marketed for and used in the research and investigation of other products. Thus, a manufacturer who labels its IVD product RUO may promote and market it for research use, for example, by general discovery laboratories. By the same token, a manufacturer who labels its IVD product IUO may promote and market it for use in a clinical investigation that is exempt from 21 CFR 812.

2. What marketing practices would FDA consider to be generally inappropriate for IVD products labeled RUO or IUO?

The mere placement of an RUO or IUO label on an IVD product does not render the device exempt from clearance, approval, or other requirements, regardless of how it is marketed. Whether it bears an RUO or IUO label, or neither, an IVD product that is not intended for research or investigational purposes would not qualify for the applicable exemptions at section 520(g) of the Act, 21 U.S.C. 360j(g) (see section II above). If such an IVD product were not cleared or approved, FDA would consider it to be 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), unless exempt from premarket notification requirements. As explained above, FDA would also consider an IVD product that is labeled RUO but not intended for research or labeled IUO but not intended for investigational purposes to be misbranded under section 502(a) of the Act, 21 U.S.C. 352(a).

In addition to overt expressions by the manufacturer such as those present in labeling and advertising, intended use may be shown by the circumstances surrounding the distribution of the product[6] [8] and the manufacturer's knowledge that its product is offered and used for a purpose for which it is neither labeled nor advertised. For example, FDA may consider a manufacturer’s knowledge of the purposes for which its customers offer and use its IVD product, and the manufacturer’s provision of technical support for those activities, to be evidence that the IVD product is intended to be used for such purposes. The weight of this evidence will vary with the circumstances.

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

- Written or verbal statements in any labeling, advertising, or promotion of the IVD product, including any performance claims, clinical information, product names, or descriptors, that claim or suggest that the IVD product may be used in a clinical investigation or for any clinical diagnostic use;
- Written or verbal statements in any labeling, advertising, or promotion of the IVD product that suggest that clinical laboratories can validate the test through their own investigational procedures and subsequently offer it for clinical diagnostic use as a laboratory developed test;
- Sales to clinical laboratories that the manufacturer knows, or has reason to know, use the IVD product in clinical diagnostic use in an investigation or otherwise, and support (including technical support) for those activities.
- Past history of promotion of the product

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] [9] 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 using it in clinical diagnosis, it should halt such sales or comply with FDA requirements for IVD products, including premarket review requirements, if applicable. FDA fully supports the use of IVD products labeled RUO for research purposes, but since these products may not be manufactured in accordance with current Good Manufacturing Practice (cGMP) and their performance characteristics have not been established, we believe they present a serious potential risk to the public health when used in clinical laboratories to generate tests results intended for patient management.

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 labeled IUO were to assist in the validation or

verification of the performance of a test that the manufacturer knows is used in non-investigational clinical diagnosis using its IUO-labeled IVD, FDA would consider such assistance to be evidence of non-investigational 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).

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[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] Although Laboratory Developed Tests (LDTs) are IVD products, for the purposes of this guidance document, "in vitro diagnostic product" or "IVD product" does not include LDTs. However, manufacturers of LDTs may find this guidance helpful in determining the proper use of IVD products labeled RUO and IUO.

[4] Throughout this guidance document, references to "clinical diagnostic use" and "use in clinical diagnosis" include use in making treatment decisions. The use of tests on organ or tissue donor specimens is considered to be a clinical diagnostic use when the results of the test are applied to make recipient management or transplant decisions.

[5] See, e.g., 21 CFR 801.4 regarding its reference to objective intent and the circumstances surrounding an article's distribution.

[6] See, e.g., 21 CFR 801.4.

[7] For purposes of this guidance, clinical laboratories include blood establishments as defined in 21 CFR 607.3(c) ("*Establishment* means a place of business under one management at one general physical location. The term includes, among others, human blood and plasma donor centers, blood banks, transfusion services, other blood product manufacturers and independent laboratories that engage in quality control and testing for registered blood product establishments.") and establishments as defined in 21 CFR 1271.3(b) ("*Establishment* means a place of business under one management, at one general physical location, that engages in the manufacture of human cells, tissues, and cellular and tissue-based products.").

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