

E-ALERT | Food & Drug

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FDA ISSUES DRAFT GUIDANCE REGARDING RESEARCH USE ONLY AND INVESTIGATIONAL USE ONLY IN VITRO DIAGNOSTIC PRODUCTS

On June 1, 2011, FDA issued a draft guidance document addressing the commercial distribution and use of in vitro diagnostic (“IVD”) products labeled for research use only (“RUO”) and investigational use only (“IUO”).¹ This draft guidance indicates that FDA is seeking to expand the scope of its authority with significant implications for device manufacturers and clinical laboratories.

While FDA stated that it issued the draft guidance in order to “remind” manufacturers of the requirements applicable to RUO and IUO products,² in fact, the draft guidance proposes new limitations on the scope of these categories and on the sale and marketing of such products. Among other provisions, the guidance advises manufacturers to cease sales of RUO and IUO products to a customer if the manufacturer learns that the customer is using the products for a clinical diagnostic use. These limitations, if adopted by FDA in a final guidance, could have a significant impact on manufacturers of IUO and RUO products, as well as on researchers and laboratories that utilize such products.

FDA advised that comments on the draft guidance should be submitted within 90 days (August 30, 2011) from the date of publication in the Federal Register.³

I. BACKGROUND

FDA’s regulations define RUO products as IVDs “in the laboratory research phase of development.”⁴ These products must be labeled “For Research Use Only. Not for use in diagnostic procedures.” IUO products are used “for product testing prior to full commercial marketing” and must be labeled “For Investigational Use Only. The performance characteristics of this product have not been established.”

FDA has stated – both in the current draft guidance and previous documents – that the classification of an IUO or RUO product is based on the exemption from the investigational device exemption (“IDE”) requirements under 21 C.F.R. § 812.2(c)(3). That provision exempts certain investigational IVDs from the requirements of an IDE, so long as certain conditions are met, including that the test is “not used as a diagnostic procedure” without confirmation of the result by a medically established diagnostic product or procedure.

Beyond these minimal regulations, FDA’s policies toward RUO and IUO products have been expressed mostly in draft guidance documents and enforcement actions. In 1991, FDA issued a

¹ Draft Guidance for Industry and FDA Staff - Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions (June 1, 2011) (hereafter “Draft Guidance”). Available [here](#).

² *Id.* at 5.

³ 76 Fed. Reg. 31615 (June 1, 2011).

⁴ 21 C.F.R. § 809.10(c)(2).

letter to manufacturers of RUO and IVO products announcing its intention to take enforcement action against products that were being distributed for clinical use.⁵ FDA followed this letter in 1992 with a draft compliance policy guide (“CPG”), and then additional draft CPGs in 1996 and 1998.⁶

Until now, the 1998 draft CPG has served as the most comprehensive source of FDA’s policies toward RUO and IVO products. According to this document, an RUO product is intended for the “laboratory research phase of development,” which may include research on “animal or human tissues.”⁷ The draft CPG “strongly encouraged” (but did not require) that manufacturers of RUO and IVO products develop a “certification program,” through which the manufacturer would obtain agreements from customers stating that they will not use the device for purposes inconsistent with the RUO or IVO classification.⁸

II. THE DRAFT GUIDANCE DOCUMENT

The draft guidance document is in the form of introductory text followed by a question-and-answer format. It addresses two broad issues: (1) the characteristics of RUO and IVO products, and (2) the conditions under which these products may be marketed or sold.⁹

A. Characteristics of RUO Products

According to FDA, manufacturer-initiated studies of RUO products are typically intended “to evaluate design, limited-scale performance, and issues such as usability of the test.”¹⁰ Examples would include “[t]ests that are in development to identify test kit methodology, necessary components, and analytes to be measured,” and “[r]eagents under development to determine production methods, purification levels, packaging needs, shelf and storage life, etc.”¹¹ The Draft Guidance recognizes that instruments and stand-alone software can also be labeled as RUO products.¹²

The agency acknowledges that RUO products may be used for “non-clinical laboratory research” for goals other than developing a commercial IVD product. According to FDA, these uses may include “developing novel and fundamental medical knowledge related to human disease and conditions.”¹³

⁵ Letter from Ronald M. Johnson, Director, Office of Compliance and Surveillance, CDRH, to Device Manufacturers (Oct. 17, 1991).

⁶ FDA, Draft Compliance Policy Guide: Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation, Chapter 24 – Devices (1992); FDA, Commercialization of Unapproved In Vitro Diagnostic Devices (IVDs) Labeled for Research Use Only or Investigational Use Only (CPG 7124.32), Sec. 300.800, Sub Chapter 300 (1996) (hereinafter “1996 Draft CPG”); Draft Compliance Policy Guide: Commercialization of In Vitro Diagnostic Devices (IVDs) Labeled for Research Use Only or Investigational Use Only – Draft, Chapter 3, Sub Chapter 300 (Jan. 5, 1998) (hereinafter “1998 Draft CPG”).

⁷ 1998 Draft CPG at 10.

⁸ *Id.* at 10, 14.

⁹ FDA states that, for purposes of this draft guidance, the term “IVD product” does not include laboratory developed tests. Draft Guidance at 5 n.3.

¹⁰ Draft Guidance at 7.

¹¹ *Id.* at 7-8.

¹² *Id.* at 8, 13.

¹³ *Id.* at 8. It is not clear whether FDA was trying to distinguish research uses that do not involve medical or health applications from basic research in the medical/health field by using the language “novel and fundamental medical knowledge,” or whether this statement was intended as a limitation on the types of research to which RUO products may be applied. To the extent that an RUO product is used for non-clinical applications, such as non-clinical research unrelated to the development of a device or other FDA-regulated product, it is not clear that FDA would have jurisdiction over such a product at all. Indeed, FDA’s use of the

FDA states that the “RUO” labeling “is meant to serve as a warning that products so labeled should not be used in clinical diagnosis or patient management.”¹⁴ FDA also suggests that clinical laboratories that develop and offer laboratory developed tests (“LDTs”) “may find this guidance helpful in determining the proper use of IVD products labeled RUO and IUO.”¹⁵

The guidance states that “[a]ny IVD product that is intended for use in a clinical investigation or clinical diagnostic use outside an investigation” should not be labeled RUO.¹⁶ FDA’s view on how it will assess the “intended use” of an RUO product is discussed below.

B. Characteristics of IUO Products

The draft guidance states that products labeled IUO are diagnostics that are themselves “the subject of an investigation,” but meet the criteria for an exemption to the requirement of obtaining an IDE. An investigational IVD may be exempt from the requirements applicable to investigational devices in Part 812 if the investigation meets the criteria set forth in 21 C.F.R. § 812.3(c)(3). That section requires that the 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.

If these conditions are met, the product may also be exempt from the general labeling requirements for an IVD if it is labeled as an IUO, including the statement “For Investigational Use Only. The performance characteristics of this product have not been established.”¹⁷

The draft guidance states that “[a]ny IVD product that is intended for non-investigational purposes, such as in clinical diagnostic use outside of an investigation, should not be labeled IUO.”¹⁸

C. Marketing and Distribution of RUO/IUO Products

The draft guidance addresses conditions for the marketing and distribution of RUO and IUO products, taking a very broad view of the type of evidence that FDA will consider in defining the “intended use” of a product.

FDA explains that, “[i]n 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 and the manufacturer’s knowledge that its product is offered and used for a purpose for which it is neither labeled nor advertised.”¹⁹ As an example, FDA says it will consider the “manufacturer’s knowledge of the purposes for which its customers offer and use its IVD

term “RUO IVD product” is inconsistent with the regulatory definition of an IVD product in 21 C.F.R. § 809.3(a), which defines an IVD product as “intended for use in the diagnosis of disease or other conditions.”

¹⁴ Draft Guidance at 8.

¹⁵ *Id.* at 5 n.3.

¹⁶ *Id.* at 8,

¹⁷ *Id.* at 8-9 (citing 21 C.F.R. § 809.10(c)(2)(ii)).

¹⁸ *Id.* at 9.

¹⁹ *Id.* at 10 (citing 21 C.F.R. § 801.4).

product, and the manufacturer's provision of technical support for those activities, to be evidence" of the intended use of the product.²⁰

According to FDA, examples of marketing practices that could establish an unlawful intended use for an RUO product include:

- statements claiming or suggesting a clinical investigative or clinical diagnostic use;
- past promotional practices;
- statements suggesting that clinical laboratories may validate an RUO product "through their own investigational procedures and subsequently offer it for clinical diagnostic use as a laboratory developed test;"²¹
- sales to clinical laboratories "that the manufacturer knows, or has reason to know, use the IVD product in clinical diagnostic use . . . and support (including technical support) for those activities."²²

Examples of inappropriate marketing for IUO products parallel the RUO examples, but allow for clinical investigational use (where RUO does not). They are:

- statements claiming or suggesting that an IUO product may be used in non-investigational clinical diagnostic use;
- past history of promotion of the product;
- statements claiming or suggesting that an IUO product may be used in a manner inconsistent with the requirements applicable to an exempt investigation under 21 C.F.R. § 812.2(c);
- sales to clinical laboratories "that the manufacturer knows, or has reason to know," use the IUO product in "non-investigational clinical diagnostic use" or in a non-exempt investigation "and support (including technical support) for those activities."²³

Likewise, FDA states that it "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," thereby rendering the device misbranded.²⁴

FDA states that the agency is aware that many manufacturers and distributors sell RUO products to clinical laboratories with knowledge that the laboratories "sometimes use [the RUO products] in clinical diagnosis."²⁵ According to the draft guidance, if a manufacturer learns that a laboratory is using an RUO or IUO product for clinical diagnosis, "it should halt such sales or comply with FDA requirements for IVD products, including premarket review requirements, if applicable."²⁶

FDA's draft guidance states that the manufacturer should not assist in the validation or verification of a test featuring an RUO or IUO product that the manufacturer knows is used in clinical diagnosis.²⁷

²⁰ *Id.* It is not clear whether FDA is saying that the manufacturer's knowledge alone would be sufficient evidence of a clinical diagnostic use, or whether an additional action such as providing technical support is an essential element of the evidence of "intended use."

²¹ *Id.*

²² *Id.* at 10.

²³ *Id.* at 11.

²⁴ *Id.* at 12.

²⁵ *Id.* at 11.

²⁶ *Id.* (emphasis added).

²⁷ *Id.* at 13.

As FDA explains, if a manufacturer assists in the validation or verification of the performance of an RUO-labeled test that the manufacturer knows is used in clinical diagnosis, FDA “would consider such assistance to be evidence of non-research intended use.”²⁸

Unlike FDA’s 1998 Draft CPG, the new draft guidance does not recommend that manufacturers implement a certification program. Nor does the draft guidance even mention the use of such certifications.

III. IMPLICATIONS AND QUESTIONS RAISED BY THE DRAFT GUIDANCE

FDA’s draft guidance, and in particular, its statements regarding a manufacturer’s intended use, raise significant issues and questions for stakeholders, including manufacturers of RUO/IUO products, researchers, and clinical laboratories.

Stakeholders likely will view FDA’s interpretation of “intended use” as unduly expansive. Although 21 C.F.R. § 801.4 purports to determine “intended use” through “circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised,” courts have traditionally taken a more limited interpretation of the concept.²⁹ The draft guidance thus departs from the principle that a manufacturer determines the intended use of its products through its own objective actions. Instead, FDA’s statements suggest that a manufacturer’s products may become misbranded or adulterated by virtue of the actions of downstream users.

In addition, FDA’s proposed policy could present significant compliance challenges. From a manufacturer’s perspective, it is unclear when or how a manufacturer will be deemed to have knowledge that one of its products is being used for clinical purposes. For example, does this policy suggest that manufacturers have a duty to determine how customers are using products? What if the manufacturer distributes its products through a wholesaler, who in turn distributes to laboratories? Will a “certification” from a customer (as recommended by the 1998 draft CPG) be sufficient, even if other facts suggest that the laboratory may be using the reagent for clinical purposes? Will laboratory customers have to prove to manufacturers that they are using RUO and IUO products for non-clinical uses, and if so, how will they do so?

FDA’s statement that manufacturers may not provide “technical support” for clinical uses also presents challenges. Manufacturers may frequently provide support for products that could be used for both clinical and non-clinical uses. If a laboratory or researcher were to request, in an unsolicited manner, information about clinical uses of an RUO product, may the manufacturer answer the question? If it does so, would that constitute “knowledge” that the customer is using the product for clinical purposes?

From the perspective of laboratories, the draft guidance also raises significant issues. As an initial matter, FDA’s draft guidance has implications for the practice of medicine and FDA’s apparent attempt to regulate it. For example, if a product is legally marketed when introduced into commerce by the manufacturer, the statute limits FDA’s authority to interfere with the prescription or

²⁸ *Id.*

²⁹ *E.g., Brown & Williamson Tobacco Corp. v. F.D.A.*, 153 F.3d 155, 163 (4th Cir. 1998) (noting that no prior court had found an “intended use” of a product absent manufacturer claims as to that use), *cert. granted*, 526 U.S. 1086 (1999), *aff’d*, 529 U.S. 120 (2000); *Assoc. of Am. Physicians & Surgeons v. F.D.A.*, 226 F. Supp. 2d 204, 218 (D.D.C. 2002) (summarizing that the long-established foundation of federal food and drug law allows “not the FDA, but the manufacturer of the article, through his representations in connection with its sale, [to] determine the use to which the article is to be put” (internal quotations and citations omitted)).

administration of the product by a healthcare practitioner.³⁰ In addition, under the Clinical Laboratory Improvements Amendments (CLIA) and implementing regulations, a clinical laboratory can use a test system “not subject to FDA clearance or approval” or “in which performance characteristics are not provided by the manufacturer,” provided that the laboratory establishes performance characteristics for the laboratory developed test.³¹ FDA has previously recognized that products labeled as RUO have been used to develop LDTs.³² Given that many LDTs are used to address important public health concerns, if FDA’s policy results in manufacturers cutting off a supply of RUO reagents, this could have an adverse impact on the public health. FDA’s policy also could have significant implications for innovation in diagnostics, particularly in the quickly growing area of personalized medicine.

Stakeholders have until August 30, 2011, to submit comments. Covington & Burling LLP has extensive experience regarding the regulation of in vitro diagnostic products and will continue to monitor developments regarding this issue.

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³⁰ 21 U.S.C. § 396.

³¹ 42 C.F.R. § 493.1253.

³² 1996 Draft CPG at 2 (stating that the CPG does not apply to “home brew” tests regulated under CLIA).