FDA Warning Letter Tightens Reins On 'Research Only' Labels

By **Scott Liebman, Dominick DiSabatino and Audrey Mercer** (April 22, 2024)

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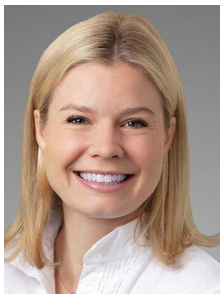

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On April 2, the U.S. Food and Drug Administration posted a warning letter to Agena Bioscience Inc., alleging that Agena's product was both "adulterated" and "misbranded" under the Food, Drug and Cosmetic Act as being labeled for research use only, or RUO, but, allegedly, promoted for human clinical purposes.

Despite the increasing prevalence of RUO-labeled diagnostic devices,[1] the FDA has issued a relatively limited amount of guidance on the development and distribution of such products. So, this warning letter adds important, and impactful, clarification to the FDA's policy on the issue.

Ultimately, the warning letter is part of a larger movement by the FDA to focus on diagnostic products that have historically been exempt from regulatory oversight.[2]

Devices properly labeled "RUO" are in vitro diagnostic devices intended to be used solely during the laboratory research phase of product development. RUO devices are considered low risk because, as the FDA has established, they may not be used for any human clinical purposes or be promoted in any manner suggesting that a human clinical use may be acceptable.[3]

As such, these products are exempt from almost all of the FDA's medical device regulations,[4] including the Investigational Device Exemption regulations, which are largely focused on ensuring the safety and efficacy of devices used for human clinical purposes.

Even though FDA regulations outline only a few narrow parameters for RUO-labeled in vitro diagnostic devices,[5] the agency has provided just one single guidance — the RUO guidance — to elaborate on the brief requirements established in the regulations.[6]

For over a decade, manufacturers of RUO-labeled diagnostic devices have relied almost exclusively on the RUO guidance to determine the parameters for developing and distributing their products. So, the FDA's letter to Agena is a curveball, potentially expanding the scope of marketing practices that the FDA considers evidence of intended clinical use.

Agena previously manufactured and sold the IMPACT Dx System, which the FDA cleared for marketing in 2014. Because the IMPACT Dx System was FDA-cleared, it was sold for clinical diagnostic use. However, the company has since discontinued the IMPACT Dx System and replaced it with a new system — the MassARRAY4, or MA4 System.

The MA4 System is marketed with accompanying chemistry panels, including the iPLEX HS Colon Panel, and is labeled "RUO." Accordingly, Agena did not submit a Section 510(k) premarket notification or premarket approval application before marketing the product.

The FDA found that the iPLEX Panel was misbranded and adulterated under the FDCA[7] because the panel is intended for use with the RUO-labeled MA4 System, yet evidence suggests that it may be intended for clinical — as opposed to research — use.

To support its conclusion that the iPLEX Panel and MA4 System are actually intended for clinical use, the FDA cites:

- Statements made by Agena personnel, as well as customer lists and distribution records, which indicate that Agena sells the MA4 System and reagent panels to clinical testing laboratories;
- A customer notification for the iPLEX Panel sent to a clinical testing hospital with no evidence that the panel was intended for research use;
- The iPLEX Panel User Guide, which includes instructions for preparing and testing samples, and instructions for interpreting the iPLEX Panel; and
- Certain statements made on Agena's website, including customer testimonials, which, according to the FDA, suggest that the product might be appropriate for clinical use.

Takeaways

Overall, the FDA takes issue with the fact that Agena's RUO disclaimers are "inconsistent" with certain representations made by Agena, which suggest that the MA4 System and iPLEX Panel may be used as effective in vitro diagnostic devices — i.e., used for clinical diagnostic purposes.

Zooming in, two observations about the form of the FDA's response to Agena's alleged violations may be particularly meaningful.

First, the FDA made a statement by issuing a warning letter instead of a less severe form of communication. And second, the FDA cited an extensive list of alleged marketing violations, including product sales to clinical customers, which may or may not have research capabilities, and the use of relatively broad promotional language.

According to FDA procedure, the agency issues warning letters "only for violations of regulatory significance," while "untitled" letters and "it has come to our attention" letters are utilized when a regulated entity engages in activity that "potentially" violates the FDCA, but that does not "meet the threshold of regulatory significance for a warning letter."[8]

Even though the FDA has only issued a limited amount of instruction on the types of evidence that might prove an RUO-labeled product is intended for clinical use, the agency chose to hit Agena with a warning letter, rather than a softer form of communication. This suggests that the FDA may have seen Agena's alleged violations as an opportunity to continue shaping its policy on RUO-labeled diagnostic devices without having to issue a new guidance document or proposed rule.

The FDA spent a considerable amount of ink elaborating on the way that Agena markets the MA4 System and iPLEX Panel. The RUO guidance specifically states that when a product has a history of distribution for clinical diagnostic use, and the product is subsequently labeled

for RUO "without any change in distribution practices such as advertising to and solicitation of business from clinical laboratories," the subsequent RUO labeling is likely to be inconsistent with the manufacturer's intended use.[9]

Agena's circumstances appear to closely align with this specific example from the RUO guidance, as FDA insinuated in the warning letter, Agena previously marketed the IMPACT Dx System for clinical use and replaced it with the RUO-labeled MA4 System, while continuing to market its product offerings (previously, the IMPACT DX System and now the MA4 System) to clinical customers for use with at least one panel promoted for clinical use (i.e., the iPLEX Panel for use with the MA4 System).

So, while the FDA could have made short work of its warning by pointing to its guidance on presenting a device with a history of diagnostic use as an RUO, the warning letter instead sends a clear message to Agena, and to the industry at large — the FDA is paying close attention to manufacturers' specific marketing activities when it comes to RUO-labeled products.

The marketing violations cited by the FDA represent a reinforcement, and a potential narrowing, of the agency's policy on RUO-labeled diagnostic devices in two significant ways.

First, the warning letter cites Agena's sales of the MA4 System and iPLEX Panel to "companies who analyze patient samples that are used for clinical diagnosis" and "clinical testing laboratories." This is consistent with the RUO guidance, which states that solicitation of business from clinical laboratories — i.e., laboratories that generate test results from human-derived specimens intended for patient management[10] — may be evidence of intended clinical use.[11]

However, the RUO guidance gives an example that includes an important qualifier, stating that the manufacturer of an RUO-labeled product "whose sales force makes routine calls to clinical laboratories that do not perform research" may be viewed as promoting the product for clinical purposes.[12] This qualifier is important, as it could be read to permit the sale of RUO-labeled products to mixed laboratories — i.e., laboratories that conduct research in addition to clinical diagnostic testing.

The language used in the warning letter, on the other hand, does not include such a qualifier, so it is not clear whether the customers on Agena's distribution lists were strictly clinical laboratories, or whether they were mixed laboratories. Therefore, while the warning letter is effective in reinforcing the FDA's position that RUO-labeled products may not be solicited and/or sold to clinical laboratories, it remains unclear whether the same is true for mixed laboratories.

Second, the promotional language cited by the FDA as evidence of intended clinical use is a stretch, to say the least. For example, the FDA points to Agena's claim that the iPLEX Panel can "detect more than 80 clinically relevant variants." Although the statement uses the words "clinically" and "relevant," the statement does not necessarily indicate that the panel is intended for clinical use.

After all, during the laboratory research phase of product development, a laboratory would likely want to tailor the assay for eventual use with clinically relevant endpoints, as opposed to clinically irrelevant endpoints. Ultimately, it appears that the FDA wants manufacturers of RUO-labeled products to be explicitly clear that the products may be used only for research purposes, leaving no room for misinterpretation.

Zooming back out, this warning letter appears to be another step in the FDA's larger initiative to ensure the safety and efficacy of diagnostic products, especially those diagnostic products that have traditionally been fairly free from FDA oversight. As the industry well knows, in September 2023, the FDA published a proposed rule that, if finalized, would end the agency's long-standing policy of enforcement discretion for laboratory-developed tests, or LDTs, a category of clinical diagnostic products that has also historically been lightly regulated.[13]

As explained in the proposed rule, widespread reports of faulty diagnostic tests, specifically LDTs, that arose in the wake of COVID-19, served as a major impetus for the FDA's push to implement more stringent oversight of diagnostic tests. This is especially the case with respect to tests that have historically been marketed without such oversight, including LDTs and RUO-labeled diagnostics.[14]

As evidenced by the LDT proposed rule and this warning letter, among other FDA actions, the FDA has set its sights on reining in diagnostic tests that are reaching the market — and in many circumstances, patients — without being proven safe and effective through established market pathways.

Ultimately, the warning letter presents more questions than answers.

For instance, will Agena challenge the letter? Will other manufacturers request advisory opinions to clarify the parameters on the development and distribution of RUO-labeled products? Is the onus on manufacturers to determine the operations of laboratory customers before soliciting business? If so, how many resources must manufacturers expend to make this determination? May manufacturers sell RUO-labeled diagnostics to mixed laboratories?

While manufacturers of RUO-labeled diagnostic devices wait on answers to these and other questions, it may be prudent to begin reviewing customer lists and promotional claims to ensure that marketing activities cannot be construed as potentially condoning clinical use.

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[1] RUO-labeled products are being produced and sold by some of the industry's largest players. See, e.g., Roche's Hepatitis B RUO Assay.

[2] See, e.g., Press Release, FDA and CMS: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made, FDA and CMS (Jan. 18, 2024).

[3] See Draft Guidance for Industry, Commercially Distributed In Vitro Diagnostic Products

Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions, FDA p. 8 (2011).

[4] See 21 CFR Part 800 et seq.

[5] See 21 CFR § 812.2(c)(3) and § 809.10(c), which establish that an investigational IVD device qualifies as an RUO product only if the product is intended for use in testing that: (i) is non-invasive, (ii) does not require an invasive sampling procedure; (iii) does not "introduce energy" into the subject; (iv) does not serve a diagnostic function unless the diagnosis is confirmed by another medically-established diagnostic product or procedure, and (v) is limited to the laboratory research phase of product development; and prominently labeled "For Research Use Only. Not for use in diagnostic procedures."

[6] See Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only, Guidance for Industry, FDA (Nov. 25, 2013).

[7] See FDCA § 501(f)(1)(B).

[8] See Letters to Industry, Center for Devices and Radiological Health (current as of Feb. 20, 2024).

[9] See RUO Guidance, supra FN 6, at p. 10.

[10] Although FDA does not directly define the term "clinical laboratory," FDA's intended meaning for the term can be gleaned from the Agency's discussion of clinical laboratories in the Draft RUO Guidance and its definition of "clinical investigation." See Draft RUO Guidance, supra FN 3, at p. 11; 21 CFR § 50.3(c).

[11] See RUO Guidance, supra FN 6, at p. 9.

[12] See id.

[13] See 88 Fed. Reg. 68006 (Oct. 3, 2023).

[14] See, e.g., 88 Fed. Reg. 68012.