FDA Draft Guidance Would Restrict Marketing of Research Use Only and Investigational Use Only In Vitro Diagnostic Products

On June 1, 2011, the Food and Drug Administration ("FDA") issued a draft guidance document setting forth the agency's proposed interpretation of the law regarding commercially distributed in vitro diagnostic ("IVD") products labeled for research use only ("RUO") or investigational use only ("IUO"). The draft guidance calls into question certain common views regarding how RUO and IUO products may be marketed. Most controversially, it asserts that manufacturers who become aware that a laboratory customer is using an RUO or IUO product for clinical diagnostic purposes should cease sales of the product to that customer. This draft guidance document has the potential to alter business practices both of manufacturers of RUO and IUO products and the laboratories that purchase and use them. FDA is accepting comments on the draft guidance until August 30, 2011.

Products Labeled as RUO

According to FDA regulations, IVD products in the laboratory research phase of development are exempt from most regulatory requirements applicable to IVD medical devices if they are labeled "For Research Use Only. Not for use in diagnostic procedures." Among other things, such products are exempt from FDA premarket approval, premarket notification (510(k) clearance), and good manufacturing practice requirements. The draft guidance clarifies the scope of RUO products, dividing them into two categories. The first category includes those products intended to assist with the development of a commercial IVD product. For this type of RUO product, the laboratory research phase of development involves manufacturer studies focused on the evaluation of the IVD test's design, limited-scale test performance, and test usability. The second category includes products intended to aid in the discovery and development of basic medical knowledge related to human disease. The draft guidance specifies that products should not be labeled as RUO if they are intended for use in a clinical investigation or for clinical diagnostic use.

Products Labeled as IUO

FDA regulations establish a separate category of certain IVD products that are intended for use in clinical investigations. Under FDA's investigational device exemption ("IDE") regulations, a clinical study of an IVD product is generally exempt from IDE requirements if the product (1) is non-invasive, (2) does not require invasive sampling that poses significant risk, (3) does not introduce energy into a subject by design or intention, and (4) is not be used for diagnosis without confirmation by another medically established diagnostic procedure or product. IVD products tested in such IDE-exempt clinical studies may appropriately be labeled as IUO and are exempt from certain IVD requirements in addition to the IDE requirements. The label for an IUO product must read, "For Investigational Use Only. The performance characteristics of this product have not been established."

Marketing Practices for Products Labeled as RUO and IUO

According to the draft guidance, labeling a product as RUO or IUO is insufficient to ensure that the product qualifies for the applicable regulatory exemptions. To qualify, the manufacturer must *intend* for the product to be used for research or investigational use only. According to FDA, the agency may determine the

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manufacturer's intended use based not only on statements in the product's labeling and advertising, but also circumstances surrounding the product's distribution and the manufacturer's knowledge that the product is offered and used for a particular purpose. Thus, FDA is asserting that the manufacturer's intent can be established based on what its customers actually do with the product, not merely based on how the manufacturer promotes it.

The draft guidance states that FDA considers the following marketing practices to be "generally inappropriate" for products labeled RUO or IUO:

- **Certain statements in labeling, advertising, or promotion.**
    - *RUO products*. Statements suggesting that the product may be used in clinical investigations or for clinical diagnosis or that a clinical laboratory can validate the test using its own investigational procedures and then offer it as a laboratory developed test for clinical diagnosis.
    - *IUO products*. Statements suggesting the product may be used for non-investigational clinical diagnosis or suggesting a use that is inconsistent with an exempt investigation.
- **Sales to certain clinical laboratories.**
    - *RUO products*. Sales to clinical laboratories that the manufacturer knows, or has reason to know, use the product for clinical diagnosis, and support for such activities.
    - *IUO products*. Sales to clinical laboratories that the manufacturer knows, or has reason to know, use the product for non-investigational clinical diagnosis or for a non-exempt investigation, and support for such activities.

The draft guidance emphasizes that a manufacturer should not sell an RUO product or an IUO product to a laboratory that the manufacturer knows will use such product for clinical diagnostic purposes. If a manufacturer becomes aware that a laboratory to which it sells an RUO or IUO product is using that product for clinical diagnosis, the draft guidance asserts that the manufacturer should either halt such sales or subject the test to premarket review and other regulatory requirements for IVD devices.

The draft guidance states that if a manufacturer promotes IVD components, instruments, or reagents that are labeled RUO or IUO for use in a laboratory developed test known to the manufacturer to provide non-investigational clinical results, FDA will consider such promotion to be evidence of an intended use in conflict with RUO and IUO labeling. Additionally, according to the draft guidance, a manufacturer of an RUO or IUO product should not assist with validation and verification of the performance of a test that uses the product and that the manufacturer knows is used for clinical diagnosis or, in the case of an IUO product, non-investigational clinical diagnosis. FDA may deem a product misbranded and adulterated as a result of any such assistance.

According to the draft guidance, a manufacturer may provide general instructions for use with an RUO or IUO product in certain circumstances; however, the draft guidance notes that products in the research phase of IVD development are unlikely to need instructions for use. Additionally, the draft guidance states that instructions regarding an RUO product should not contain information regarding clinical interpretation or clinical significance, which FDA interprets as suggesting a non-research use for the product.

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Implications for RUO and IUO Manufacturers

FDA's draft guidance, if finalized, would significantly impact RUO and IUO product manufacturers, limiting the ways in which they can promote and sell their products. It would also impact laboratories that have been in the practice of developing and validating clinical tests using RUO and IUO components. One potentially controversial restriction is the provision stating that RUO and IUO product manufacturers should not inform laboratories that they have the ability to design, assemble, and validate their own "home brew" clinical tests using RUO or IUO components, subject to regulation by the Centers for Medicare and Medicaid Services ("CMS") under the Clinical Laboratory Improvement Amendments ("CLIA"). Also likely to be controversial is the assertion that manufacturers have a duty not to sell RUO or IUO products to a laboratory that they learn has used such products for clinical diagnostic purposes.

FDA has issued the draft guidance document for comment purposes only. Nevertheless, it appears that the draft guidance reflects FDA's *current* views on the law and the meaning of its RUO and IUO regulations. What remains unclear is whether FDA would proceed to take enforcement action based on the kinds of practices described above before finalizing the guidance. Doing so could leave the agency open to challenges for failure to follow appropriate administrative procedures. FDA will be accepting comments on the draft guidance until August 30, 2011.

If you would like to discuss the foregoing or any other related matter, please contact any member of Ropes & Gray's FDA Regulatory Practice or your usual Ropes & Gray advisor.

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