American
Clinical Laboratory
Association

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VIA ELECTRONIC SUBMISSION (www.regulations.gov)

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

RE: Docket No. FDA-2011-D-0305
Draft Guidance for Industry and FDA Staff: Commercially Distributed In Vitro Diagnostic Products labeled for Research Use Only or Investigational Use Only: Frequently Asked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

Dear Sir or Madam:

The American Clinical Laboratory Association ("ACLA") is pleased to provide comments to the Food and Drug Administration ("FDA") on issues related to the draft guidance entitled, "Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions" ("Draft Guidance").

ACLA is an association representing clinical laboratories throughout the United States, including local, regional, and national laboratories. ACLA members perform various types of clinical diagnostic testing, including laboratory developed tests ("LDTs"), some of which may incorporate Research Use Only ("RUO") or Investigational Use Only ("IUO") labeled components or use general purpose reagents or instrumentation that a manufacturer might erroneously have labeled as RUO or IUO. As a result, ACLA members will be directly affected by the Draft Guidance.

We appreciate FDA's solicitation of stakeholder input as it considers how to proceed regarding the treatment of marketed products labeled as RUO or IUO.[1] We share FDA's commitment to ensuring the appropriate use of all components of clinical testing. However, we are concerned about some of the assumptions made in the Draft Guidance and the potential impact of these erroneous assumptions on laboratories and the physicians and patients who rely on these commonly-used clinical diagnostic testing services. In particular, ACLA believes that

[1] Although the terms "RUO" and "IUO" are often used interchangeably, in fact, in most instances where concerns arise, it is with products that are incorrectly labeled "RUO", because that label represents the easiest regulatory pathway for manufacturers to use.

the Draft Guidance ignores the fact that the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which regulate virtually all clinical laboratories performing testing, requires laboratories to establish performance specifications and validate any test that is not FDA-approved or cleared. As a result, ACLA submits that where the laboratory complies with the requirements of CLIA, the use of a properly validated RUO or IUO product should be permitted.

At the outset, ACLA notes that FDA has stated clearly that the Draft Guidance does not apply to LDTs. FDA states that, "[a]lthough [LDT] 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."[2] ACLA is pleased that FDA clearly states that the Draft Guidance is not intended to apply to LDTs; however, it must recognize that some LDTs are developed using RUO or IUO components. Therefore, notwithstanding the disclaimer on LDTs, this FDA Guidance will have a significant impact on some LDTs and the laboratories that offer them. Further, ACLA does not accept FDA's characterization of LDTs as "IVD products" or its assertion that LDTs are "manufactured." Clinical laboratories offer LDTs as diagnostic testing services, which are regulated under CLIA, and not as manufactured products. LDTs are not manufactured, nor are they sold as devices.

As set out in more detail below, ACLA has three major suggestions for improving the Draft Guidance. First, FDA should acknowledge that laboratories operating under CLIA are permitted to use RUO/IUO products if the laboratories comply with applicable CLIA requirements, including those related to validation of the tests. Second, FDA should exercise care in this area, because many of the tests using RUO/IUO reagents are in fact standard of care today, and any precipitous action likely would have the unintended consequence of hurting patients; therefore, if it decides to act in this area, FDA should consider a lengthy grace period during which manufacturers are allowed to come into compliance. Third, FDA should recognize that it is the manufacturer, not the laboratory, that decides how to label these products and reagents; therefore, FDA should encourage manufacturers to take steps to label devices appropriately, as required by FDA regulations.

I. Testing Services Offered by Clinical Laboratories are Validated under CLIA

FDA's main concern as expressed in this Draft Guidance appears to be that manufacturers are improperly making available RUO/IUO products, which laboratories may then use in diagnostic tests. For example, in the Draft Guidance, FDA states:

> 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.[3]

[2] Draft Guidance at page 5, n.3.
[3] Draft Guidance at 5.

FDA further states that it—

> 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.[4]

ACLA believes that it is erroneous to conclude that the use of RUO/IUO products in LDTs leads to tests with "unproven performance characteristics." FDA makes a significant error in that it does not recognize that laboratories specifically are permitted under CLIA to use test systems that have not been approved or cleared by FDA. CLIA specifically sets standards for laboratories that either modify FDA-approved or cleared test systems or that introduce test systems not subject to FDA clearance or approval, including "methods developed in house."[5] Under 42 C.F.R. § 493.1253, laboratories are required to establish performance specifications for such tests, which provide assurance of the test's appropriateness. Thus, CLIA was designed in such a way to permit laboratories to utilize products that did not have FDA approval or clearance, such as RUO and IUO products, so long as the laboratory establishes the performance characteristics for the test and the test is properly validated in accordance with CLIA.[6]

While the Draft Guidance differentiates between LDTs and IVD products for purposes of the document, some manufacturers of RUO and IUO products may interpret this guidance in such a way that they will cut off sales of all RUO and IUO products to laboratories. Because clinical laboratories must establish the performance characteristics and fully validate LDTs under CLIA, we disagree with any assumption that marketing of RUO and IUO products to laboratories results in diagnostic use of laboratory tests with unproven results. Characterization of diagnostic test results as "unproven" is inconsistent with the CLIA requirements that laboratories establish the performance specifications of and validate the tests they offer.

FDA should recognize that the safety and validity of LDTs offered by CLIA-certified laboratories is highly-regulated under CLIA, even where RUO and IUO products make up components of fully-validated testing services. The CLIA regulatory scheme was designed to address the unique nature of the laboratory industry, including LDTs, which are not regulated by FDA. Therefore, in final guidance, FDA should state that it would exercise its enforcement discretion in situations where RUO/IUO products are sold to laboratories that properly validate the resulting tests, in accordance with CLIA.

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[4] Draft Guidance at 11.

[5] 42 C.F.R. § 493.1253 (b)(2).

[6] We note also that the New York State Department of Health does permit laboratories to use RUO and IUO products after review by the Department to determine the extent to which the manufacturer has established the performance characteristics of the assay, and only after written approval from the Department. *See* State of New York Department of Health, Comprehensive Test Approval Policy and Submission Guidelines (February 2011), *available at* http://www.wadsworth.org/labcert/TestApproval/forms/Submission_Guidelines_Policy.pdf.

In the interest of continuing improvement in patient safety, ACLA would be happy to work with both FDA and CMS to enhance the existing CLIA framework by identifying particular approaches to validation, quality assurance and control, and result report disclaimers for LDTs utilizing RUO and IUO components that could be adopted as best practices under CLIA.

II. LDTs Performed using RUO and IUO Products Provide Significant Value

In the Draft Guidance, FDA takes the position that manufacturers should not sell any RUO or IUO products to laboratories if they know that the laboratory is using the product in clinical diagnosis. As noted above, this approach is inconsistent with CLIA, which specifically permits laboratories to validate tests developed in-house, using components or instruments not requiring FDA clearance or approval.

Further, many LDTs that are critical to standard patient care today include RUO and IUO elements. For example, many newborn screening tests today routinely employ RUO and IUO components. Newborn screening uses tandem mass spectrometry, where the instrumentation, software, and reagents are not FDA-cleared or approved. If the manufacturers of these products were suddenly to stop selling to laboratories, these routine, yet critical, screenings would come to a halt. Other examples include DNA sequencing for all genetic disorders, array comparative genomic hybridization (array CGH) that is replacing traditional cytogenetics as standard of care for evaluation of children with developmental delays, molecular oncology disorders such as quantitative BCR/ABL for CML, and quantitative PML/RARA for APL. In addition, virtually all genetic tests for diagnosis of hereditary disease use RUO reagents (primers, buffers, etc.) and instruments (thermocylcers, sequencers). Similarly, array-based testing relies on both instruments and software that may be labeled as RUO. Even the instruments used to extract DNA from clinical samples are labeled as RUO. Other LDTs using RUO and IUO components that have become standard of care in patient management and now appear in medical organization position statements, clinical practice guidelines, and medical textbooks include the following:

- Inhibin A
- Inhibin B
- Adiponectin
- Anti-68kD
- Tetanus Antitoxin Antibodies
- HBV DNA testing
- Chromogranin A
- Human Chorionic Gonadotropin
- Proinsulin
- Acetylcholine Receptor Blocking Antibodies
- Neopterin
- Neuron Specific Enolase
- Pancreatic Polypeptide
- Vasoactive Intestinal Polypeptide
- Voltage-gated Calcium Channel Antibody
- Von Willebrand Multimers
- Factor XIII Activity
- Von Willebrand Factor Collagen Binding Protein

In sum, many tests today that are offered in full compliance with CLIA regulations and are considered standard of care utilize RUO/IUO reagents; thus, any precipitous action by FDA could have the effect of denying patients access to needed services.

III. FDA Should Allow a Reasonable "Grace Period" to Avoid Disruptions in Patient Care

In discussions with the agency regarding regulation of LDTs generally, FDA has recognized the importance of not inhibiting innovation in this rapidly developing area. ACLA is concerned that precipitous action in this area could work to the detriment of patients who benefit from this testing, which often relies on RUO and IUO components, where such testing is validated in accordance with CLIA requirements. Given the widespread use of LDTs that include RUO and IUO components, ACLA believes it is vital that FDA proceed cautiously and thoughtfully in this area to avoid creating barriers to patient access to important diagnostic testing services.

While ACLA believes that laboratories acting in conformance with CLIA should be permitted to use RUO/IUO products, manufacturers should be encouraged to obtain FDA approval or clearance of these same devices. However, manufacturers will need time to come into compliance with FDA's requirements in this area. For example, it will require some time and effort for manufacturers to comply with the Quality System Regulation (QSR) or to change labeling for general purpose products that are labeled erroneously as RUO or IUO. Given the importance of these products as components of laboratory-developed tests used in patient care, we believe there would be significant unintended consequences if FDA finalizes guidance to require that a manufacturer stop selling these products until it complies with FDA requirements for IVD products, including premarket review requirements, if applicable. A grace period should apply for laboratory test components, instruments, and kits currently labeled RUO/IUO.

ACLA believes that FDA should work with manufacturers to address some of the concerns cited in the Draft Guidance and provide time for them to come into compliance. To the extent that products currently labeled as RUO or IUO in fact meet the definition of an Analyte Specific Reagent (ASR), manufacturers should be given time to work with FDA to amend product labels while laboratories continue to use these products. ACLA recommends that FDA encourage manufacturers to list and label reagents as ASRs where possible, which would further the agency's goals of encouraging manufacturers to produce reagents in QSR facilities rather than using the RUO/IUO label where it is not appropriate.[7]

In the final version of the Guidance, we also encourage FDA to address the fact that many instruments commonly used in laboratory medicine may in fact be mislabeled as RUO or IUO under current FDA requirements. If FDA is going to require these devices to be approved or cleared when used by the laboratory for a particular purpose,

[7] In some instances, FDA could alleviate some of the current issues if it allowed more products to qualify as ASRs. Because of the very restrictive definition of an ASR, which is limited to a product that is used to detect a single ligand or target, some manufacturers may instead use the RUO label. However, if the FDA permitted manufacturers to label products as ASRs that were simply a combination of ASRs, manufacturers would not use the RUO label, and, just as importantly, the products would then be manufactured in accordance with QSRs.

that process will be lengthy and complex. In fact, however, it would be preferable for FDA to recognize that many of these instruments simply should be considered general purpose instruments that are sold, and used, for a variety of purposes within a laboratory. They are labeled as RUO only because the FDA appears to be requiring manufacturers to obtain approval or clearance for virtually any conceivable intended use. It would be far more reasonable if FDA permitted these devices to be sold and labeled for general use, with the recognition that it is up to the laboratory, under CLIA, to validate their use. In this way, manufacturers would not be forced to label them RUO inappropriately. Such an approach would avoid the calamitous effects of precipitous action, which could affect the ability of laboratories to obtain needed instruments, as well as to obtain maintenance, software and other updates, and even supply parts.

In order to continue to meet these various concerns, ACLA recommends that FDA offer a grace period to allow manufacturers to work with FDA to revise their labeling and to come into compliance. Given the thousands of products potentially involved, this Guidance could generate a large number of clearance requests, which FDA will have to review. Given FDA's own workload and limited resources, we believe a grace period of at least three years will likely be necessary to prevent hurting patient care.

IV. RUO and IUO Products are Marketed by Manufacturers, not by Laboratories

Finally, ACLA notes that the Guidance appears to suggest that laboratories are using these RUO and IUO products without the knowledge of the manufacturer. In fact, it is the manufacturer who determines to use the "RUO" or "IUO" label, rather than utilizing other more appropriate FDA pathways. As laboratories need these reagents for testing that they develop and offer—much of which is state of the art, as discussed below—the laboratory has little choice but to accept the product as labeled. Further, because clinical laboratories operate in compliance with CLIA, which permits them to offer LDTs if the laboratory establishes the performance characteristics and the tests are properly validated, laboratories are not in violation of FDA requirements in offering the tests. Various statements made in the Draft Guidance that suggest otherwise are inaccurate, mislead the public and should be removed from the final published guidance document.

ACLA is concerned about the FDA's emphasis throughout the document on what manufacturers knew or should have known about the laboratory's use of RUO or IUO products. This approach is likely to create practical difficulties for all parties, as it will require the manufacturer to try to evaluate the laboratory's intent with regard to the products at issue. In the past, manufacturers sometimes attempted to shift the responsibility to the laboratory, by seeking certifications concerning how they intended to use the products at issue. ACLA fears that this Draft Guidance simply will create new barriers, because manufacturers will attempt to obtain new assurances from laboratories to protect themselves from FDA scrutiny. ACLA believes that FDA should repudiate the use of such certifications as a way for the manufacturer to protect itself; rather,

manufacturers should be strongly urged to go through the proper FDA procedures and correctly label these same products.

Again, ACLA submits that the best solution to this issue is for FDA to recognize that laboratories are permitted to utilize RUO and IUO products consistent with CLIA. This will alleviate many of the regulatory concerns that will otherwise arise from FDA's formulation.

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Thank you for the opportunity to comment on this Draft Guidance. If you have questions or need any further information, do not hesitate to contact us.

Sincerely,

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