College of American Pathologists

Comments to the
Food and Drug Administration
on the draft guidance
Commercially Distributed In Vitro Diagnostic Products
Labeled for Research Use Only or Investigational Use Only:
Frequently Asked Questions

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The Food and Drug Administration (FDA) released a draft guidance entitled, "Commercially Distributed in Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions". The guidance clarified the regulatory requirements applicable to in vitro diagnostic (IVD) products intended for research use only (RUO) or investigational use only (IUO). In addition, the guidance serves as a warning that products so labeled should not be used in clinical diagnosis or patient management.

The College of American Pathologists (CAP), *celebrating 50 years as the gold standard in laboratory accreditation,* is a medical society serving more than 17,000 physician members and the global laboratory community. It is the world's largest association composed exclusively of board-certified pathologists and is the worldwide leader in laboratory quality assurance. The College advocates accountable, high-quality, and cost-effective patient care. CAP Laboratory Accreditation Program is responsible for accrediting more than 7,000 clinical laboratories worldwide. Our members have extensive expertise in providing and directing laboratory services and also serve as inspectors in the CMS-deemed CAP accreditation program. CAP also provides laboratories with a wide variety of proficiency testing programs and has the responsibility to evaluate the accuracy of test performance and interpretation in more than 23,000 laboratories worldwide.

RUO/IUO GUIDANCE

High quality laboratory developed tests (LDTs) have been in clinical use for many years and represent some of the most innovative tests offered to patients today. CAP believes that use of RUO and IUO reagents, instruments, and systems, as components of LDTs, should be permissible in clinical diagnosis and patient management when reasonable substitutes are not available. CAP supports the FDA's efforts to ensure consistency and reliability of diagnostic tests; however, we assert that performance of LDTs can be safely assured through the CLIA certification, accreditation and inspection processes, proper assay validation and ongoing proficiency testing. These programs are designed to ensure the quality of laboratory services and the accuracy and reliability of test results. Moreover, CAP shares the FDA's commitment to public health and believes that regulatory efforts should focus on ensuring the integrity of LDT performance, not the composition of components.

Limiting RUO/IUO usage will hinder patient care by significantly interfering with medical treatment options available to clinicians. As physicians specializing in the diagnosis of disease through laboratory methods, pathologists have a long track record of delivering high quality diagnostic services to patients and other physicians and have a keen interest in ensuring that these services are not overly restricted.

CONCERNS

RUO/IUO Products

The language of this draft guidance defines RUOs/IUOs as in vitro diagnostics products, which are assay systems, assay component reagents and instrumentation. Each product type has separate issues that CAP believes should be addressed differently by the Agency.

- RUO/IUO assay systems: These assay systems are produced by manufacturers and utilized by clinical laboratories, with labs taking responsibility for assay validation and all performance characteristics including accuracy and precision.

- Instruments: General laboratory equipment is used in clinical laboratories. Examples of general laboratory equipment include sequencers, thermal cyclers, general electrophoresis equipment, centrifuges, microscopes, scanners, spectrophotometers, pH meters, incubators, water baths, slide stainers, coverslippers, flow cytometers etc. The clinical laboratories perform daily checks, quality control and quality assurance, as well as maintenance.

- RUO/IUO component reagents: General reagents, such as molecular reagents, Taq polymerase, restriction enzymes, monoclonal antibody, and customized microarrays are sold to both research and clinical labs. These reagents are combined with other components as part of LDTs to provide a service for our patients. Virtually all genetic testing, prenatal screening, histocompatibility and identity testing use such reagents. The labeling of these reagents as RUO/IUO can vary widely among individual suppliers.

Quality of Care/Patient Access

The College believes that the draft guidance will negatively impact patient care especially in areas of hematology, tumor immunology and chemotherapy, prenatal diagnosis, women's reproductive health, prenatal screening, genetic testing, and histocompatibility testing. Moreover, the RUO/IUO guidance will adversely impact patient care that uses diagnostic techniques such as flow cytometry. For instance, virtually all hematolymphoid malignancies such as leukemia and lymphoma use flow cytometers with RUO/IUO fluorescent reagents as a standard diagnostic practice. The ability of hematologists and oncologists in the U.S. to diagnose and treat patients would be certainly compromised without the RUO/IUO availability.

In addition to their use in diagnosis and treatment selection among prenatal, pediatric, and cancer patients, RUOs/IUOs are often used in the diagnosis of rare diseases. Due to low testing volume, manufacturers would not find it economically feasible to develop products for rare diseases if FDA clearance or approval is required. As a result, the College believes that the draft guidance will have a negative impact on patient care especially in areas such as genetic testing and histocompatibility testing which a single recipient or single donor is tissue typed.

Of similar concern are reagents that are provided by a single manufacturer. Single source RUOs/IUOs are used in many clinical laboratory disciplines such as genetic testing and prenatal screening. For example, the pregnancy associated plasma protein A (PAPP-A) is sold by only one or two vendors in the USA and is used in first trimester and integrated prenatal screening for Down syndrome. This test is one component of a well-established LDT that is fully incorporated into routine clinical practice. Approximately 1,000,000 patients per year are currently being tested with panels that include PAPP-A measurements. The latest 2009 American Congress of Obstetricians and Gynecologists (ACOG) practice bulletin recommends offering these prenatal panels to all pregnant women.

Validation of Performance Characteristics for LDTs

This draft guidance poses a major concern for clinical laboratories performing LDTs because of the implication that LDTs that use RUO/IOU have 'unproven performance characteristics' and may mislead healthcare providers and cause serious adverse health consequences to patients. Clinical laboratory tests in accredited laboratories are closely regulated to ensure that all testing meets accepted performance characteristics. Each clinical laboratory is required under CLIA to verify the analytic validity of every diagnostic test. In doing so, the laboratory establishes analytic sensitivity, analytic specificity, accuracy, precision, reportable range and reference intervals. Further, for CAP-accredited laboratories, all molecular testing systems must have clinical validity established as well. CAP believes that clinical laboratories offering tests using RUO instruments, software, and reagents can recognize the potential problems and through strict adherence to quality management and assay validation establish a high degree of assurance of test quality.

Many organizations besides CAP have developed testing and practice standards and guidelines for laboratory testing including the American College of Medical Genetics (ACMG), Clinical and Laboratory Standards Institute (CLSI), New York State Department of Health, the Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR), laboratory accreditation and proficiency testing. The College believes that proficiency testing is a valuable means to monitor laboratory performance. There is a strong and convincing evidence base for the effectiveness of

laboratory-developed tests utilizing RUO/IUO and ASR reagents in routine settings in the United States, Europe and elsewhere. In addition, the CAP and ACMG jointly evaluate analytical and interpretive test performance of both US and international laboratories. Overall, clinical laboratories perform very well, with evidence that US labs have excellent performance, and are performing even better than the overall average derived from national and international labs combined.

Need for a phased-in approach

The guidance is intended for manufacturers and distributors of RUO and IUO IVD products, however the guidance will have a profound impact upon diagnostic laboratories. Should RUO/IUO reagents and instruments be simultaneously removed from the market, clinical laboratory testing in many disciplines will no longer be available and greatly impact patient safety and public health. The College acknowledges the benefits of products manufactured under the FDA's current good manufacturing practices (cGMP) but believes RUO/IUO products should be addressed differently. The College supports the FDA's intent to require clearance/approval for assay systems that are marketed as RUOs/IUOs but believes the FDA's approval pathway for such systems needs to be clear and consistent. However, for RUO/IUO reagents and instruments that have proven track records, the FDA should employ "enforcement discretion" policy regarding use of these assays and instruments.

CONCLUSION

The College fears that a strict interpretation of the draft guidance entitled, "Commercially Distributed in Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions" will disrupt clinical laboratory testing and negatively impact patient care. Many of the RUOs/IUOs currently employed in clinical laboratories have well established and determinative roles in clinical care. The College is also concerned that the interpretation will reverse many recent gains in laboratory medicine, hinder innovation and reduce the speed of test development.

CAP Recommendations

CAP believes in order to minimize disruptions in patient care and ensure continued patient access to high quality tests, the Agency needs to adopt a flexible approach to enforcement and that a time window to implement changes is critical. During that window, these products need to be available to clinical laboratories to avoid a negative impact on patient care. CAP also emphasizes that the Agency adopt an enforcement discretion policy for RUO/IUOs reagents since it is expected that laboratory-developed tests (LDTs), which incorporate these reagents, will soon be subject to enhanced FDA oversight. Finally, the CAP recommends the FDA consider the financial burden to clinical laboratories of re-packaging widely-used reagents that will require re-validation of the LDTs,

CAP appreciates this opportunity to submit these comments on the draft guidance document. If you have any questions, please do not hesitate to contact, Helena Duncan, Assistant Director, Public Health and Scientific Affairs (202.354.7131/hduncan@cap.org).

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