



Association for Molecular Pathology
Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology

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Division of Dockets Management
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To whom it may concern:

Thank you for the opportunity to submit these comments to the draft guidance document titled, *Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions*. The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 1,900 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics and genomics. Membership includes professionals from the government, academic medicine and the *in vitro* diagnostics industry.

AMP members are dedicated to the development and implementation of molecular pathology testing, including genetic testing, in a manner consistent with the highest standards established by the Clinical Laboratory Improvement Amendments (CLIA '88), the College of American Pathologists (CAP), the American College of Medical Genetics (ACMG), and the Food & Drug Administration (FDA). Laboratory developed tests (LDTs) are an essential and central component of medical practice. AMP supports the development of tests and test systems for *in vitro* diagnostic use (IVDs) and encourages industry to pursue FDA clearance and approval where current regulations require review.

AMP, however, is very concerned that this guidance, if enforced in its broadest sense without sufficient accommodations for low test volume or sufficient time for manufacturers to achieve submission compliance, could compromise the quality of patient care by severely reducing the availability of certain reagents and laboratory developed testing services that have become the standard of care for many diseases or conditions. Reduced availability of testing services would limit a healthcare provider's ability to manage patient care, and ultimately limit patient access to new or improved molecular tests.

Some products used for laboratory tests are available only as RUO or IUO products. AMP supports FDA clearance and approval of RUO and IUO products, especially test kits and test systems. However, to prevent disruption of patient care, accommodations should be made to ensure continued patient access to critical tests as manufacturers come into compliance and/or

instances where low test volume would deter a manufacturer from submitting an application to the FDA for that product. For example, the vast majority of instruments, software and reagents for sequencing assays are not cleared or approved by the FDA and sold to laboratories as research use only (RUO) or investigational use only (IUO) products. In another example, this guidance document could dramatically limit access to high resolution HLA testing, which would have numerous consequences to patient care. Additionally, newborn screening programs rely heavily on RUO and IUO instruments, reagents and software in their testing services and as currently drafted, this guidance document could remove or restrict access to some newborn screening, increase costs beyond the limits of States' already over-burdened budgets, and temporarily create shortages of tests. Last, 3.2 million Americans have chronic HCV infection.¹ Most hepatitis C genotyping tests are performed using RUO and IUO products. This guidance could severely limit access to these and other standard-of-practice laboratory tests used to make essential patient management decisions.

Moreover, AMP is not aware of 'problems' associated with RUO/IUO tests beyond levels associated with other general and specialty laboratory tests (to include FDA-cleared assays). Cumulative statistics from CAP proficiency surveys show that laboratory-developed tests which use RUO/IUO-labeled reagents and ASRs perform well and equivalently to FDA-cleared test systems where such exist.

While AMP appreciates the FDA concern over the use of RUO and IUO products in LDTs, the Association questions the underlying assumption that the guidance will encourage most manufacturers to seek clearance and approval for their RUO and IUO products. The advent of ASRs enabled laboratories to use commercial products for patient benefit that would otherwise not be available. However, AMP believes that some requirements for ASRs, *e.g.*, that they be only a single analyte, with no exceptions, have contributed to the increase of RUOs for clinical diagnostic use. Accommodations should be made to enable certain reagents such as primer or probe mixes to be sold as ASRs. Alternatively, another regulatory pathway could be designed for products that are too complex to qualify as ASRs but are not full test kits or test systems.

AMP members fear that instead of seeking FDA review, some manufacturers will choose to withdraw RUOs from the clinical market. This has already occurred for many analytes, from blood-borne pathogens to sexually transmitted diseases. This would then create a shortage of supplies to develop laboratory tests, resulting in a scarcity of tests, and ultimately, barriers for patients' access to medically necessary tests.

As noted in our comments to CDRH in June 2010², AMP believes that serious barriers often exist that can impede the path to approval and reduce the motivation to submit some medically useful tests. Manufacturers have faced uncertainty and/or inconsistency in the review of device submissions, in enforcement discretion, in device classification [510(k), 510(k) *de novo*, PMA, ASR, etc.], in requirements for acceptable analytical and clinical validations, and in requirements changing from the time of pre-IDE meetings through mid-trial. Manufacturers must then

¹ Center for Disease Control and Prevention, data downloaded 7/26/2011 from <http://www.cdc.gov/hepatitis/HCV/index.htm>.

² Association for Molecular Pathology Comments to FDA's Center for Devices and Radiological Health (CDRH) Council on Medical Device Innovation: Barriers to Market for Molecular Diagnostic Tests, available online at http://www.amp.org/Position%20Statements/AMPCComments_FDAMedicalDeviceWorkshop_062410_final.pdf

function within this uncertain regulatory environment and are limited in their efforts to anticipate regulatory requirements and appropriately amend business plans.

AMP strongly encourages the FDA to consider the downstream implications of the guidance on supplies and materials for laboratory testing, and allow for circumstances where clinical laboratories can develop tests using RUO and IUO products when no other products are available.

Finally, AMP also asks the FDA to clarify which products are included in the guidance document. In clinical laboratories, instruments and general reagents such as distilled water and buffer solutions may or may not be labeled RUO or IUO. Does the FDA intend to require these components of LDTs to be subject to FDA review?

AMP's recommendations include:

1. To avoid the disruption of patient care, carefully consider enforcement discretion or alternative regulatory pathways to address circumstances where no FDA cleared/approved products are available, particularly for those products with limited sales volume.
2. Direct enforcement requirements for 510(k) or PMA submissions toward test kits and test systems.
3. Create a consistent and clear pathway to encourage and facilitate ASR, 510(k) or PMA applications for RUO and IUO products, with a reasonable compliance timeline. The pathway must include flexibility to be responsive to rapidly evolving areas.
4. Accommodations should be made to enable certain reagents such as primer or probe mixes to be sold as ASRs. Alternatively, another regulatory pathway could be designed for products that are too complex to qualify as ASRs but are not full test kits or test systems.
5. Clearly state the scope of the guidance. Clarify which products currently labeled as RUOs and IUOs the guidance covers, e.g., test kits, instruments, software, and reagents.

AMP supports FDA's mission to "promote and protect" public health, balancing safety concerns with access and availability of exciting new medical breakthroughs. Thank you again for your consideration of AMP's comments and we look forward to working with the agency to develop guidelines that will both protect patients and promote the development of molecular pathology.

Sincerely,
Elaine Lyon, PhD
Chair, Professional Relations Committee