



Association for Molecular Pathology

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

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The Association for Molecular Pathology (AMP) would like to provide comments to the Food and Drug Administration on the recently issued draft guidance: ***Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions*** (Docket # 2006D-0336), published on September 7, 2006

AMP is an international not-for-profit educational society representing over 1,400 physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on nucleic acid technology. AMP members practice their specialty in widely diverse settings: academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the *in vitro* diagnostic industry. In this capacity, AMP members are involved in every aspect of molecular diagnostic testing: administration and interpretation of molecular diagnostic tests, research and development, and education. For the last several years, AMP has provided national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry.

AMP's Mission Statement identifies the Society as "dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics." Our goal is to represent all members regardless of the setting in which they practice because they are united in the end intent to provide high quality, relevant information for the purpose of directing individual and patient community health management. We acknowledge, however, that different perspectives may emerge from those widely diverse settings. In those instances, our primary responsibility is to comment from the standpoint of molecular testing laboratories and the patients they serve.

AMP acknowledges what we believe to be FDA's stated intent in issuing this guidance. 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. AMP, however, is very concerned that this guidance, if enforced in its broadest sense, could severely reduce the availability of certain reagents and laboratory developed testing services, and compromise the quality of molecular test development by laboratories under CLIA, which have become the diagnostic or prognostic 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. AMP requests that, for significant changes to the ASR rules or interpretation of those rules, the rulemaking process be used in an open, public forum.

The advent of ASRs enabled laboratories to use commercial products for patient benefit that would otherwise not be available. The goal of the ASR rule was to promote quality and consistency in the manufacture of ASRs; to clarify for the healthcare provider ordering tests and using the test results for patient management that certain tests developed using ASRs were not reviewed by FDA; to restrict sale and distribution to high complexity laboratories with persons qualified in test development; and to limit labeling and promotional material to identity and purity

of the reagent (i.e., with no stated performance characteristics). The stated purpose of the draft guidance is to provide clarification of existing ASR requirements. Operationally, the guidance appears to present new interpretations of the existing requirements that have not been enforced since the publication of the rule in 1997.

AMP makes the following points regarding FDA's draft guidance on ASRs for consideration as the agency prepares a final document.

- **AMP supports FDA's original premise that ASRs should not be sold with an intended use or performance characteristics of the final test; and that use should be restricted to CLIA-certified high complexity laboratories.**
- **AMP requests that FDA clarify whether the purpose of an ASR is to identify a single disease or condition (which would require multiple single chemical substance ASRs in combination) or whether an ASR is a single chemical substance. The two definitions are mutually exclusive for most molecular tests; the second one describing a substance that will not detect any chemical moiety in a molecular test when used in isolation and is not optimal for test development and validation in a clinical molecular pathology laboratory.**
- **AMP emphasizes that limiting the definition of ASRs to a single chemical substance should not be applied to molecular ASRs because two or more unique reagents (e.g. separate PCR primers) are typically required to identify a single analytic target in most molecular tests. For this reason, ASRs should be allowed to include the minimum necessary set of reagents.**

The vast majority of molecular tests require the use of more than one "ASR" (under this restrictive definition), such as two primers and one or more probes at a minimum, "to identify one specific disease or condition" (stated as the purpose of an ASR in the preamble to the ASR rule, 62 FR 62243, 62244). In reality, a single primer does not meet the criteria for an ASR because by itself, a single primer cannot identify any chemical substance target or gene. Since these reagents must be used in combination to perform a single test, the ASRs required for a single test should be able to be sold as a group. Preventing the manufacturer from providing complete information to the laboratory about the design and use of a group of reagents intended to identify a target, gene or infectious agent, severely compromises the quality of laboratory test development, validation, and standardization. If manufacturers can provide information about the appropriate combination of ASRs, (and general purpose reagents (GPRs)) required for detection of a single chemical substance, e.g. a single mutation in a gene, or provide a grouping of multiple reagents to detect all mutations that may cause a single disease or condition, then this significantly enhances the ability of the laboratory to validate a test under CLIA using a set of ASRs and GPRs sold by a single manufacturer. The laboratory must still validate the performance of these reagents under CLIA, regardless of the sale of reagents as single entities or as a group.

- **AMP requests that FDA emphasize the improvement in the quality of reagents that the ASR rule makes available to clinical laboratories.**

The FDA Draft Guidance may lead to manufacturers producing fewer ASRs, or current ASRs may be removed from the market. ASRs do provide a level of standardization and quality that is of value to laboratories developing their own tests.

- **AMP is concerned that the narrower interpretation of the ASR rule will result in decreased availability of ASRs, including currently used ASRs, with a resulting decreased availability of now standard-of-care tests, future molecular tests, and**

decrease patient access to these tests that will be critical for optimal patient management and care.

AMP is concerned that the implementation of the ASR draft guidance as currently written will severely impact access to commercial reagents that are routinely used in hundreds of tests, which will have a negative impact on the delivery of medical care. There are numerous molecular tests performed using ASRs. Tests for infectious diseases include the diagnosis of neurologic disease due to HSV, VZV and enterovirus; quantitative testing for monitoring CMV, EBV and BK viruses in transplant recipients; detection of *Bordetella pertussis*; HCV genotyping; and the detection of respiratory viruses. Genetic and oncology tests performed using ASRs include those for gene translocation analysis, genetic aneuploidy, microdeletion syndromes, and bone marrow engraftment analysis. (See Attachment A for a limited list of laboratory-developed genetic tests based on ASRs.) These tests, which are performed as laboratory-developed tests, affect the health care of many patients every day. Numerous peer-reviewed publications citing use of these assays have revealed that the vast majority of laboratory-developed tests using ASRs (manufactured under cGMPs) and fully validated in the laboratories of board-certified molecular genetics and molecular pathology laboratory directors under CLIA regulations, are extremely robust, accurate and reliable; in most cases, more so than the laboratory-developed assays these tests replaced. Consistency of results between laboratories has also been improved. Thus, the sudden removal of these ASRs from the market or even limiting the availability of these high quality reagents would not only impact patient access but would seriously compromise the quality of molecular diagnostic testing nationwide, with likely harm to patients. The impact will be most severe regarding reagents used to diagnose rare diseases.

- **AMP requests that manufacturers be allowed to communicate appropriate information about the sets of ASRs required for detection of a single disease or condition, using peer-reviewed literature citations as appropriate and available.**

Medical laboratory professionals must know the target gene region or nucleic acid sequences of a reagent in order to properly design and validate (both analytically and clinically) a clinical test. Further, much of the literature will contain methods descriptions that enable laboratories to validate another laboratory's procedure and results. This test validation process for laboratory-developed tests is still required under CLIA regulations. Therefore, it is to the benefit of the laboratory and the patients they serve that literature references be freely distributed to support the reliable use of the ASR.

- **AMP suggests that FDA allow manufacturers to distribute basic assay recommendations that would enable laboratories to more expeditiously establish optimal assay conditions and simultaneous testing standardization across different laboratories. The wording of the basic assay recommendations could emphasize that the conditions must be optimized by each laboratory for specific instruments and laboratory practices.**

Some ASRs requiring multiplexing to identify a single disease or condition that can be caused by multiple genetic variants or organisms. Therefore, "an individual ligand" should be defined in a context that makes scientific and clinical sense.

For example, an infectious disease test uses two primers, one probe and an internal control designed to assure the test performs appropriately. The combination of all these reagents is required for identification of the individual infectious disease ligand. This should not be considered a multiplex test.

- **AMP does not believe that co-marketing of ASRs with controls, general purpose reagents, general purpose instruments or off-the-shelf software detracts from the**

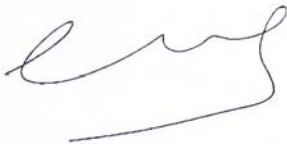
safety of these reagents, as long as the system is open for optimization and validation by the individual laboratory. In fact, AMP strongly believes that this enhances the quality of laboratory development and validation.

In systems that are truly open, laboratory directors have discretion to use whatever platform they choose, and are not obligated to purchase all materials from a single manufacturer. We do agree with FDA that “closed test systems” and/or “finished IVD devices” are problematic, as the laboratory director does not have the flexibility to design and optimize these assays. In either case, these prohibitions are not included in the ASR Rule, nor were they addressed in the preamble to the rule. As a result, AMP believes that these changes would also require notice-and-comment rulemaking.

- **AMP supports FDA enforcement against manufacturers who sell ASRs to be used with specific instrumentation or software in a closed system. The laboratory must be able to manipulate the conditions of a test and review raw data during test development, validation and performance. AMP agrees that closed systems are appropriately categorized as a test system requiring FDA review.**

Thank you for the opportunity to comment on this very important document. AMP, whose members are routine users of ASRs, is ready to work with FDA to develop clear, reasonable guidelines that will promote the development of molecular pathology. AMP supports FDA’s mission to “promote and protect” public health, balancing safety concerns with access and availability of exciting new medical breakthroughs. Please do not hesitate to contact Wayne Grody, MD, PhD, AMP Professional Relations Committee Chair at WGrody@mednet.ucla.edu if we can be of further assistance.

Sincerely,

A handwritten signature in black ink, appearing to read 'Andrea Ferreira-Gonzalez', with a long horizontal line extending from the bottom of the signature.

Andrea Ferreira-Gonzalez, PhD
President

Appendix A: Examples of Multiplex Laboratory Developed Genetic Tests based on ASRs

Gene	Clinical Application in Laboratory Developed Tests
<i>ACADM</i>	Targeted mutation analysis for aid to diagnosis of MCAD Deficiency
Ashkenazi Jewish Panel: <i>ASPA, BLM, FANCC, GBA, HEXA, IKBKAP, MCOLN1, SMPD1</i>	Per recommendations of ACOG (<i>ASPA, HEXA</i> and <i>IKBKAP</i>) and ACMG (<i>HEXA</i> and <i>ASPA</i>) for carrier screening and commercial demand for same for other loci, targeted mutation analysis for 8 loci and 31 mutations/variants. Laboratories also develop disease-specific tests based on single loci.
<i>BRCA1/BRCA2</i>	Aid to risk assessment for breast and ovarian cancer
<i>DMD</i>	Deletion/duplication analysis for carrier testing and aid to diagnosis for Duchenne/Becker muscular dystrophy
<i>FGRFR3</i>	Targeted mutation analysis for aid to diagnosis of achondroplasia
<i>GALT</i>	Targeted mutation analysis for aid to diagnosis of galactosemia
<i>MLH1, MSH2, MSH6, PMS2</i>	Microsatellite instability testing for diagnosis of HNPCC
<i>FMRI</i>	Triplet repeat expansion for carrier testing and aid to diagnosis of Fragile X syndrome; aid to diagnosis of premature ovarian failure and FXTAS
<i>HBA, HBA2, HBZ</i>	Deletion/duplication analysis for aid to diagnosis of β -thalassemia
<i>HBB</i>	Targeted mutation analysis for carrier testing and aid to diagnosis for β -thalassemia and sickle cell anemia
<i>HFE</i>	Targeted mutation analysis for carrier testing and aid to diagnosis for hereditary hemochromatosis
<i>HP</i>	Targeted mutation analysis for carrier testing and aid to diagnosis of anaptoglobinemia
Histocompatibility Loci	Donor identification and engraftment studies for transplant; disease associations as an aid to diagnosis
<i>MTHFR</i>	Assessment of obstetric risk, used in combination with F2 and F5 testing
<i>RET</i>	Targeted mutation analysis for aid to diagnosis of MEN2
<i>SERPINA1</i>	Targeted mutation analysis for carrier testing and aid to diagnosis of Alpha-1-Antitrypsin deficiency