



## Association for Molecular Pathology

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

9650 Rockville Pike, Bethesda, Maryland 20814

Tel: 301-634-7939 • Fax: 301-634-7990 • Email: [amp@asip.org](mailto:amp@asip.org) • [www.amp.org](http://www.amp.org)

### 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

The Association for Molecular Pathology (AMP) is an international medical professional association representing approximately 1,800 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 aims to educate others and advance the field of molecular diagnostics; we thank the organizers for the opportunity to express our observations and concerns regarding barriers to the development and/or redesign of *in vitro* diagnostic devices and tests.

AMP commends the Federal departments and agencies that compose the Council on Medical Device Innovation for making efforts to identify and remove barriers to innovation and progress in transitioning basic and transitional research findings into routine clinical practice. These include increased efforts to develop standards and guidelines for use in clinical laboratory medicine, as well as for use by developers of test methods and manufacturers to “baseline” the performance of, and to improve and advance, available tests.

It is important to note, however, that serious barriers often exist that can impede the path to approval and reduce the motivation to submit some medically useful tests.

**Barrier 1. The paucity of standard reference materials for all areas of molecular diagnostics, i.e., genetic, oncology, and infectious disease testing, inhibits the production of appropriate control materials and methods.** AMP is eager to see more progress and investments in this area. FDA can assist by providing a list of needed standard reference materials to relevant organizations such as the National Institute of Standards and Technology (NIST) and World Health Organization (WHO).

**Barrier 2. The difficulty of obtaining rare specimens for studies presents a barrier to submission of applications for the approval of new indications for currently approved tests.** Herpes Simplex Virus (HSV) testing has been the standard of care for the diagnosis of CNS disease (HSV encephalitis and meningitis) for over a decade, yet an FDA approved test does not yet exist. Although the clinical possibility of HSV CNS infection is commonly encountered, true infections are relatively rare, and any individual laboratory may receive only 1-2 HSV encephalitis positive specimens a year. Manufacturers who developed assays for the novel 2009 influenza H1N1 strain encountered similar difficulties in validating their assays using prospective clinical specimens after the peak of the pandemic had passed.

Possible solutions to address this problem include the establishment of a biorepository of clinically relevant infectious agents, including strain variants and subtypes, to facilitate the rapid

development and validation of assays for infectious agents, particularly those with pandemic potential. Alternatively, consideration should be given to establishing alternative validation strategies that are independent of primary clinical specimens, but are, nonetheless, rigorously grounded in sound science and infectious disease medicine.

**Barrier 3. Test manufacturers perceive that there is an inconsistent and unclear regulatory pathway for their submissions.** 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. IVD test manufacturers must then function within this uncertain regulatory environment and are limited in their efforts to anticipate regulatory requirements and appropriately amend business models.

We present several current issues that illustrate these problems.

**1. Requirements for tests for the same analyte have increased precipitously for subsequent submissions.** As an example, over the last six years the FDA has reviewed and cleared several tests for the detection of mutations associated with cystic fibrosis and blood coagulation disorders. In the review of the first molecular genetic tests (e.g. for factor V Leiden, prothrombin, and cystic fibrosis), the FDA allowed manufacturers to utilize DNA constructs and cell line DNA tested in replicates to establish the tests' performance of rare mutations for which clinical samples were difficult to acquire. However, manufacturers of subsequent tests are required to perform testing on a greater number of clinical samples for each mutation. Instead of being permitted to utilize DNA constructs and cell lines, greater numbers of clinical whole blood samples are required, even for exceedingly rare mutations. In addition, FDA added a requirement for 3 peer-reviewed papers for each new mutation for which clearance is sought, describing 3 unrelated patients' genotype and CF phenotype. The requirement for 3 papers and 5 samples has made it very difficult to validate rare mutations and is inconsistent with the original clearance criteria. Most importantly, the scientific evidence supporting these escalating requirements has not been communicated. AMP is concerned that such inconsistencies greatly deter submissions of tests for review. We recommend that requirements remain consistent and, should these requirements need to be altered, the basis for any such changes be clearly communicated.

**2. Comprehensive studies to demonstrate the clinical utility of tests that monitor therapy for viral infections are required even though clinical utility for such testing has been well established.** An important example is the regulation and classification of testing for hepatitis C virus genotype (HCVg) and viral load. The only drugs currently FDA-approved for treating HCV infection are interferon alpha (both pegylated and non-pegylated) with or without ribavirin. These drugs were reviewed and approved using clinical trial data that definitively demonstrated the dependency of sustained viral response on HCV genotype, with genotype 1 showing poor response indicated by viral load, and genotypes 2 and 3 having greater sustained virological response. In fact, the FDA-approved labeling for these drugs includes drug dosage and duration based on HCV genotyping and HCV viral load. The data supporting the clinical utility were derived using multiple genotyping and viral load methods during the clinical trials of currently approved drugs for HCV infection.

The requirement to repeat these clinical trial has become an onerous barrier for manufacturers seeking clearance for HCV genotyping tests. Although the importance of HCVg testing was demonstrated by drug trials, currently all clinical HCV genotyping performed in the United States is performed using laboratory-developed tests (LDTs). Using its enforcement discretion, the FDA requires that manufacturers of reagents used in laboratory-developed HCV genotyping assays submit their products for pre-market review as PMAs, the most stringently regulated category of IVD. FDA also requires validation studies to establish clinical performance with a significant number of clinical samples for all HCV genotypes and subtypes, whether or not they are currently found in the U.S. HCV infected population. This clinical utility work has already been completed in the earlier drug trials; therefore, the reasoning for this requirement is unclear. Moreover, this requirement conflicts with the CDER's acceptance of the clinical utility of HCV genotyping, which has been included in the approved labeling for the drugs. AMP is concerned that these requirements do not contribute to the demonstration of safety and efficacy and unduly delay the entrance of cleared products into the market, thus contributing to the persistent use of LDT.

HCV viral load testing has similar issues. The FDA requires that each company submitting an assay include clinical trial data that demonstrates clinical utility. The clinical utility of HCV viral load in managing patients receiving antiviral therapy has been well established. Requiring each manufacturer to repeat these clinical studies is overly burdensome. It is not clear how this adds to better patient care or protects patients from harm. It is worthwhile to note this type of clinical study is no longer required for HIV-1 viral load or for HIV-1 genotyping tests.

The comparison of the requirements for HCV and HIV-1 genotyping tests is an important example of perceived inconsistencies in application of the regulatory pathway. By requiring clinical utility trials for every HCVg test submitted, it seems that the FDA has deviated from its prior decision to "down-classify" HIV-1 genotyping tests a decade ago. In that instance, an FDA Advisory Panel agreed that the clinical utility of HIV-1 genotyping for use in managing patients' antiretroviral therapy had been established by four studies, each using a unique and different HIV-1 genotyping technology. Since all of the patients for which the test would be performed were already known to be infected with HIV-1, the test was not used for diagnosis or for testing the blood supply and therefore did not have the same implications for patient safety. This resulted in the down-classification of HIV-1 genotyping assays from Class III to Class II, and from PMA submissions to 510(k) *de novo* submissions. AMP does not understand why similar logic is not applicable to HCV genotyping. AMP believes that using resources (from industry, academia, patient care facilities and regulatory agencies) to re-prove demonstrated clinical utility in lower risk situations, prevents them from being better utilized to improve existing tests and to develop more tests.

**Summary: AMP believes that the FDA can take several steps that would improve the regulatory process for molecular diagnostic tests without impinging upon an appropriate review to ensure that the public is protected.**

- FDA should ensure that policies and requirements are consistently applied, and that the scientific evidence and rationale for decisions are communicated effectively to diagnostic test manufacturers.

- Communication from FDA to diagnostic test manufacturers should be as clear and as comprehensive as possible at the outset of the submission process. This will help manufacturers better plan their resources and time. It will also assuage undue angst that the regulatory bar will change during the process.
- FDA should improve communication between branches so that consistent requirements are developed and applied and demonstrations of clinical utility in one branch are recognized by the other branches.
- FDA should involve the expert opinion of medical professional associations regarding clinical utility.

The Association for Molecular Pathology recognizes the difficulties regulatory agencies face in the context of the rapidly changing landscape of diagnostic devices and technology and appreciates the transparent process FDA is undertaking to improve the review process for medical devices. AMP believes that a consistent, clear, and flexible regulatory process will result in improved public access to additional higher quality innovative tests; and could conceivably lower healthcare costs. AMP stands ready to assist the FDA through our expertise, creative problem solving, and unique perspective. We would like to offer our input and interaction with the member departments and agencies to assist in developing a more consistent, evidence-based, and transparent process for regulating diagnostic devices.