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*Advancing Excellence*

Direct Response To:

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February 22, 2002

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

Re: Docket No. 01D-0286

Dear Sir/Madam:

The College of American Pathologists (CAP) is providing written response to the Food and Drug Administration's (FDA) request for public comment on the Draft Guidance for Industry Pre-market Notifications for In Vitro Drug Resistance Genotype Assays: Special Controls (hereafter "Draft Guidance"). The CAP is a national medical specialty society representing over 16,000 pathologists who practice clinical and/or anatomic pathology in laboratories across the country. The College's Commission on Laboratory Accreditation is responsible for the accreditation of over 6,000 laboratories worldwide. CAP members have extensive expertise in providing and directing laboratory services and serve as inspectors in the accreditation program. In addition, CAP members direct laboratories that are regularly engaged in the development and performance of new types of testing, such as in vitro drug resistance genotype assays, to help monitor various medical conditions. Therefore, we have a profound interest and experience in this area.

The CAP is very concerned that the implementation of the proposed Draft Guidance would stifle HIV drug resistance genotyping testing developed by laboratories, and adversely impact patients in need of these services. The CAP asserts that there is no clear justification by the FDA to change the classification of analyte specific reagents (ASRs) used in HIV-1 drug resistance testing developed by laboratories to class III devices. These ASRs do not fit the class III definition because they are not used for diagnostic purposes. Moreover, pre-market approval requirements will seriously hamper innovation, implementation, and improvement of these important laboratory procedures.

#### **Draft Guidance May Stifle Innovation In Patient Care**

The constant introduction of new treatment strategies and new FDA approved drugs continues to drive the rapid evolution of HIV drug resistance genotyping testing. Clinical laboratories, using assays developed in-house utilizing ASRs, referred to as laboratory developed tests, are at the cutting edge of these discoveries. Laboratories that develop these in-house assays often identify

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new mutations in the HIV virus itself. It is absolutely essential that laboratories be able to continue to develop and utilize these laboratory developed assays in order to support the development of new HIV treatments, provide practitioners with important clinical information, and aid clinicians in choosing the appropriate treatment for their patients. The Draft Guidance will ultimately limit the availability of ASRs for incorporation into laboratory developed assays, a result that will harm patients in need of these laboratory services. The Draft Guidance further restricts the ability of manufacturers to sell ASRs to laboratories for use in assays developed in-house for HIV drug resistance genotyping by requiring premarket approval for ASRs used in these test systems. This drastic change in FDA policy will seriously undermine the ability of laboratories to contribute to scientific innovation in this field and will interrupt the vital flow of medical information needed for treatment of patients with diagnosed HIV. Consequently, the Draft Guidance, if implemented, will stifle the innovation that now drives quality patient care and create a serious risk of reduced access to the very highest level of testing for the patients that need it most.

### **Classification under the ASR Rule**

Since 1998, high complexity CLIA certified clinical laboratories and medical device manufacturers have been operating under the current ASR regulations, which classify most ASRs as class I devices, exempt from the premarket approval process. Classifying the ASR as a class III device requiring premarket approval constitutes a significant change in current medical practice and regulatory oversight. Since the rule classifying ASRs has been in place, laboratories and manufacturers have been working under the assumption that ASRs used in HIV drug resistance genotyping tests are class I devices. The Draft Guidance asserts that ASRs used in genotyping systems to detect HIV mutations are class III devices. This position is in direct contravention of the established ASR rules.

Since HIV drug resistance genotyping tests do not fit the class III definition because they are not used to diagnose HIV, laboratories and device manufacturers have always considered these ASRs to be class I devices. ASRs used only to monitor HIV mutations and subsequently design HIV treatments serve a purpose categorically different from ASRs used to actually diagnose HIV. The ASR regulations clearly recognize this distinction and state that ASRs used to diagnose HIV are class III. Although the Draft Guidance mistakenly assumes that ASRs used in genotyping systems to detect HIV mutations are class III devices, the ASR regulations clearly indicate that ASRs used in such tests should be considered class I devices. Thus, imposing additional levels of regulation for testing that is not intended to be diagnostic is unnecessary and may be harmful to the patient by denying him or her access to necessary testing of evolving HIV mutations.

### **In-house Laboratory Testing and CLIA**

Clinical laboratories are already subject to extensive oversight and regulation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Furthermore, the Centers for Disease Control and Prevention (CDC) has issued a notice of its intent to promulgate regulations to modify the existing CLIA regulations for even stricter oversight of genetic testing. It would be more logical and reasonable to require additional oversight of laboratory developed testing under

this existing regulatory framework instead of creating an entirely new and burdensome regulatory requirement. Laboratories conducting tests for human assessment, diagnosis and/or treatment must register with the Centers for Medicare and Medicaid Services (CMS) under CLIA '88, establish and conduct specified quality procedures, participate in proficiency testing (when available) and are subject to periodic inspection. Since the vast majority of genetic tests are developed and performed by clinical laboratories in-house, these tests are already subject to the most stringent standards under CLIA. The existing regulatory framework currently provides effective federal oversight without hindering patient access to care or unnecessarily increasing laboratory costs. Also, there are many private sector and professional accrediting programs, like the CAP, currently working within the federal framework, that provide additional oversight and guidance to laboratories performing genetic testing. Therefore, we do not believe additional FDA regulation is warranted.

The ASR Final Rule makes it clear that as restricted devices, ASRs may only be sold to manufacturers, laboratories qualified to perform high complexity testing under CLIA, or non-clinical laboratories for research or other uses. FDA agreed that the CLIA regulations regarding in-house modification of materials or methods were adequate to protect the health and well-being of patients without increasing the regulatory burden on manufacturers and laboratories; in-house modification of materials and methods fall within the scope of the practice of medicine, and a more stringent classification would hamper the provision of quality medical care to patients; and regulation of in-house modified or developed materials and methods would constrain the development of innovative and improved technologies. Furthermore, FDA stated that restricting the sale of ASRs to a particular type of laboratory was sufficient to support their safe and effective use.

In summary, the type of classification change contemplated by the Draft Guidance for these particular ASRs would create an undue burden on manufacturers of ASRs and the laboratories that depend on these products for use in in-house laboratory testing. The CAP urges the FDA to consider how the proposed change will interfere with the relationship between physicians and laboratories, disrupt current medical care, and may lead to dire consequences for patients and the public health.

The College of American Pathologists appreciates the opportunity to provide comments on this Draft Guidance. Please feel free to contact me or Phil Bongiorno, Assistant Director of Public Health and Scientific Affairs at (202) 354-7113, pbongio@cap.org with any comments or questions.

Sincerely,



Paul Raslavicus, MD, FCAP  
President