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Direct Response To:
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August 20, 2001

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061, (HFA-305)
Rockville, MD 20852

Re: Docket No. 01D-0202

Dear Sir/Madam:

The College of American Pathologists (CAP) is providing the following written response to the Food and Drug Administration's (FDA) request for public comment on the Guidance for the Least Burdensome Provisions of the FDA Modernization Act of 1997 (FDAMA): Concept and Principles; Draft Guidelines for FDA and Industry. The College 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 Laboratory Accreditation Program is a Centers for Medicare and Medicaid Services (CMS) approved accrediting organization as specified in CLIA regulations. 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, the CAP provides clinical laboratories with a wide array of proficiency testing programs and educational solutions to assist in the improvement of the laboratory's performance and its positive impact on patient care. These programs combined are designed to improve the quality of laboratory services and to ensure the accuracy and reliability of test results.

The College understands that the "Least Burdensome" concept applies to the approval of all devices and device components regulated by FDA and, when applied, is intended to help ensure scientific integrity in the decision-making process, while affording a high degree of public health protection and expediting the availability of new device technologies.

The College believes the FDA device approval process using correlation to an existing assay should be used selectively for approving new assays. When correlating test results to an existing assay, the analytic methods may not be comparable and clinical information may not

01D-0202

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be provided for the newly developed test. The College understands that not all assays require clinical trials. For example, another way of measuring sodium would likely require only *in vitro* correlation. However, for more complex systems, such as most immunoassays, the test methods are not necessarily comparable. In Immunology for example, there are many assays for antibodies to incompletely defined antigens and it is more difficult to know whether the same distribution of antibodies or antigens is being measured by different assays. In this example, *in vitro* correlation would not be an appropriate approval mechanism.

The College has observed difficulty with the use of the 510(k) approval process by manufacturers assuming that immunoassays are all equivalent, even though they use different antigens or antibodies all with quite different specificity and sensitivity. For example, there is good clinical information that a certain hemaglutination titer of antibody to rubella indicates an immune status. There are no comparative data for enzyme immunoassays. In this comparison, the critical antigens and antibodies may be different. Thus, while *in vitro* characteristics may be somewhat comparable, the clinical interpretation of the immunoassay is not possible because the appropriate clinical studies have not been performed. The other reagents in the test system are also likely to vary and they can influence both the sensitivity and specificity of the result.

For the reasons noted above, the College recommends the FDA review specific problems that have arisen in the approval of some assays. Specifically, the College recommends that the appropriate FDA review panels devote more time to defining the actual criteria for equivalence, particularly for those assays in diagnostic immunology, microbiology and transfusion medicine. We further recommend FDA revisit prior regulations for the 510(k) approval process of the same assays.

Furthermore, the National Committee for Clinical Laboratory Standards (NCCLS), a consensus organization from academia, industry and government, is in the process of finalizing a guideline, I/LA21-A - *Clinical Evaluation of Immunoassays* that details appropriate requirements for developing clinical immunoassays. The NCCLS document places far more responsibility on the part of the manufacturer for the clinical evaluation of immunoassays. The College recommends the FDA utilize this document as a standard reference in the clinical evaluation process.

Thank you for the opportunity to present the College's views. Please feel free to contact me or Phil Bongiorno, Assistant Director of Public Health and Scientific Affairs at (202) 354-7113 or pbongio@cap.org with any comments or questions.

Sincerely,

Paul Bachner, MD

Paul Bachner, MD, FCAP
President