#1395

ASRs

Public Citizen

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Joan Claybrook, President

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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr., Rm 1-23
Rockville, MD 20857

RE: Classification/Reclassification of Analyte Specific Reagents
[Docket No. 95P-0110]

I. Introduction

On behalf of Public Citizen's Health Research Group, we offer the following comments about the Food and Drug Administration's proposed classification/reclassification of analyte specific reagents (ASRs). These reagents are the active ingredients used by laboratories in the development of in-house clinical tests.

Although we commend the Food and Drug Administration for proposing regulation of at least one component of the diagnostic tests manufactured in clinical laboratories, we are concerned that controlling the ingredients rather than the final product can only lead to regulatory confusion in the future. We believe that the public health would be better served through regulating the actual test rather than its component parts.

Furthermore, we are concerned that FDA has chosen to ignore the issues raised by the Immunology Devices Panel concerning regulation of predictive genetic tests. We believe the panel's suggestions were based on substantial analysis of the complex issues surrounding genetic testing. We urge FDA to reconsider its proposed rule and classify analyte specific reagents used to predict genetic diseases or predisposition to diseases (or the laboratory tests constructed using them) into class III.

II. Background

Many clinical laboratories develop and prepare their own tests to diagnose medical conditions. These tests are assembled in-house from components purchased from biological or chemical suppliers. In addition to several components that are identical for all procedures, each test also includes a distinctive reagent designed to detect a specific analyte for a disease or condition.

Until now, neither the finished product nor the component ingredients of "in-house" diagnostic tests have been covered by Federal regulations. As a result, neither patients nor practitioners have assurance that the ingredients or the final product are of high quality and capable of producing consistent results.

In this proposed rule, FDA has outlined a classification scheme that would classify/reclassify analyte specific reagents presenting a low risk to the public health into class I (general controls). These ASRs would be exempt from the premarket notification requirements, but would be subject to the good manufacturing practices regulation and would have restrictions on their sale, distribution, and labeling. FDA also has proposed to classify or retain ASRs presenting a high risk to the public health into class III.

FDA sought public and expert review from the Immunology Devices Panel in formulating this policy. At the January 22, 1996 meeting, the advisory panel recommended this two-tiered regulatory structure, and delineated several types of products they felt should receive more rigorous review. In particular, the panel suggested that

> "those analyte specific reagents intended to diagnose communicable diseases or where the Agency has established a recommendation for use of the test in safeguarding the blood supply or establishing the safe use of blood and blood products and/or tests to predict genetic disease or predisposition to disease in healthy or apparently healthy individuals are more properly classified into Class II or III and subject to premarket controls, 510(k), or PMA as applicable to such classifications".[1]

In developing its proposed rule, the Food and Drug Administration adopted all of the advisory panel's recommendations except for those concerning genetic testing. Despite the unanimous recommendation of the advisory panel, the Food and Drug Administration discarded two points: the exclusion of human DNA in the definition of an ASR, and an exemption for predictive genetic tests.

Public Citizen is concerned that FDA has failed to recognize that predictive genetic tests present unique public health issues that require a greater level of regulatory control.

III. Response to Specific Issues Raised in the Federal Register

1. Regulation of ASRs Intended for Use in Human Genetic Testing

Genetic testing is rapidly becoming an integral part of clinical medicine. In patients with overt manifestations of illness, genetic tests can confirm or rule out potential diagnoses. They can identify the existence of disease prior to the development of acute illness, thereby allowing early, often life-saving, treatment. They can determine the likelihood of passing an inherited condition to a child, and can allow prenatal diagnoses of severe disabilities. Finally, genetic tests can predict the risk of future disease in patients who are currently healthy.

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[1]Transcript of the Immunology Devices Panel of the Medical Devices Advisory Committee meeting, January 22, 1996.

Techniques for genetic testing have evolved at a tremendous pace, with current technology allowing identification for disease-causing alleles for single-gene disorders and susceptibility-conferring alleles for common, multifactorial disorders[2]. Despite their obvious benefits, genetic tests carry overt risks not presented by more traditional types of diagnostic systems. These tests have the ability to predict risks of future disease, but these predictions rarely approach certainty. Furthermore, there is often no independent test other than appearance of the disease to confirm the prediction of a genetic test. The results of genetic testing confront patients and family members with serious ethical issues regarding life style, reproduction, and family interactions. Finally, genetic testing exposes patients to disorders that may have no intervention, treatment, or cure.

Public Citizen believes that the additional risks associated with predictive genetic testing warrant enhanced regulatory control in order to ensure a high level of public health. We believe that predictive genetic testing should not be available on any but an investigative basis until the clinical validity (i.e. sensitivity and positive predictive value) of such tests have been proven, the clinical utility of providing patients this type of information has been demonstrated, and the extent of psychosocial problems engendered by predictive testing has been assessed.

Thus we believe that ASRs used for predictive genetic testing be classified as class III devices subject to demonstration of safety and effectiveness prior to premarket approval.

Alternatively, the FDA could decide that all analyte specific reagents offer the same degree of risk. In this situation, the tests used to predict genetic outcomes should themselves be regulated as class III diagnostic devices.

2. Definition of Analyte Specific Reagent

The Immunology Devices Panel recommended that analyte specific reagents be defined as:

> "...antibodies (both monoclonal and polyclonal), specific receptor proteins, non-human nucleic acids and fragments of non-human nucleic acids, and similar biological reagents which, through specific chemical binding or reaction, are intended for diagnostic identification or quantification of specific analytes in a biological specimen."

The FDA, in its proposed rule, revised the definition to include:

> "...antibodies, both polyclonal and monoclonal, specific receptor proteins, nucleic acid sequences, and similar biological reagents which, through chemical

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[2]NIH-DOE Task Force on Genetic Testing, Working Group on Ethical, Legal, and Social Implications of Human Genome Research (1996). Interim Principles.

binding or reaction with substances in a specimen, are intended for identification and quantification of an individual chemical substance or ligand in biological specimens."

This definition omits the Immunology Devices Panel's recommendation to exclude human nucleic acids from the definition of ASR. In justifying this exclusion, FDA stated that it "is not certain that making a distinction among tests that directly identify genetic material (i.e. DNA, which the panel recommended for class II or III) as opposed to transcribed genetic material (i.e. mRNA) or gene products (i.e. proteins and post-translationally modified proteins, which the panel recommended for class I) provides a meaningful basis for differing regulatory treatment of ASRs that are used to develop these tests." FDA has appeared to misunderstand the panel's intent which was to exclude human nucleic acids because they are most often used to directly identify genetic material and thus have a much greater potential to be used for predictive genetic testing than transcribed genetic material or gene products.

Public Citizen believes that the advisory panel's intent in proposing to omit human nucleic acids in the definition was to ensure that predictive genetic testing received proper regulatory oversight. We believe that this issue should be maintained in the final regulation, but we do not believe that it is necessary to exclude human nucleic acids from the definition of an ASR. Human DNA is not the only category of ASRs capable of being used in genetic tests. Assays for enzymes and other proteins can also yield predictive information for both carriers and apparently healthy affected individuals. Consequently it accomplishes little to exclude human nucleic acids from the definition of ASRs as proposed by the Immunology Devices Panel. We therefore agree with FDA's definition of analyte specific reagents.

3. Suitability of Term "Analyte Specific Reagent"

This name is suitable for the type of product it represents.

4. Requirement of Disclaimer on Test Report

We agree that a disclaimer should accompany all reports of results from laboratory testing. The wording for this disclaimer should include:

"The test used to obtain these results was developed by [laboratory name]. Neither the laboratory test nor the procedures used to obtain these results have been reviewed by the U.S. Food and Drug Administration."

5. Availability of Tests Developed by Laboratories Using ASRs.

The issue of how to regulate ASRs used for tests requested by patients as opposed to physicians

is one example of the regulatory morass that FDA will enter if it tries to regulate components rather than complete tests. Obviously, regulating one product in several different ways depending on who will ultimately use it presents very difficult logistical problems. Ultimately, a manufacturer of an ASR has little control over how a laboratory uses its product. Regulation of ingredients used in tests requested by physicians as opposed to those requested by patients would require two sets of regulations on one product. Likewise, regulating components used to make diagnostic tests versus predictive tests is also difficult.

We believe that the best way to ensure the quality of "in-house" laboratory tests is to regulate the actual product that is produced by the clinical laboratory. In this case, laboratories would have to include usage information when they applied for FDA approval. If new uses for approved diagnostic devices were desired (i.e. using a diagnostic test for predictive applications), the laboratories would have to file a supplemental application with FDA. High quality could be ensured additionally by requiring the manufacturers of analyte specific reagents to meet good manufacturing practices rules and to comply with the basic requirements of a class I diagnostic device.

IV. Conclusion

Analyte specific reagents can be used as components in a wide range of diagnostic procedures. Some of these procedures involve significantly greater inherent risks than others. We are distressed that the Food and Drug Administration, in promulgating these proposed regulations, failed to acknowledge the complex issues posed by the Immunology Devices Panel. The major issue raised by this panel--the special regulatory control needed for predictive genetic tests--must be addressed before these regulations are set in place. Furthermore, we believe that the Food and Drug Administration has taken the wrong tactic in proposing to regulate the active ingredients rather than the finished product in the in-house manufacture of clinical laboratory tests. We believe that even with an FDA-approved active ingredient, the regulations, as proposed, allow too much room for the quality of the finished product to be inadequate.

Sincerely,

Laurel S. Mendelson, M.S.
Medical Devices Researcher
Public Citizen's Health Research Group

Sidney Wolfe, M.D.
Director
Public Citizen's Health Research Group