Guidance for Industry

Analyte Specific Reagents; Small Entity Compliance Guidance; Guidance for Industry

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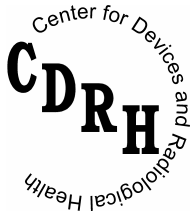
For questions regarding this document contact Steven I. Gutman, M.D., at (301) 594-3084 or by email at sig@cdrh.fda.gov.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of *In Vitro* Diagnostic Device Evaluation and Safety

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to 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. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Introduction

FDA has actively been involved in regulation of tests kits and systems since passage of the Medical Device Amendments of 1976. FDA has developed tools for premarket, compliance, and postmarket surveillance and thousands of products have entered the marketplace under these controls.

In the past, FDA was not actively involved in regulation of in-house (so-called "home-brew") tests or in regulation of the building blocks sold and used to create these tests.

In the *Federal Register* of November 21, 1997 (62 FR 62260), FDA published a final rule classifying the building blocks of in-house tests as analyte specific reagents (ASRs) and subjecting both the manufacturers of these building blocks as well as the laboratories using them to incremental regulation. The purpose of this rule was to clarify FDA oversight for in-house tests in relation to the oversight provided by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and to ensure that these building blocks would be made consistently over time according to the agency's quality system regulations. For postamendments ASRs, this rule became effective on November 23, 1998.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Summary of the Regulation

FDA developed the ASR rule to clarify FDA policy with regard to the status of in-house tests and to provide incremental controls to assure the quality of the materials being used to create these tests, to assure that laboratories preparing these tests were able to establish and maintain performance and understood their responsibility for accomplishing this, and to provide appropriate labeling so that healthcare users would understand how these tests were being validated. The rule defined the active ingredients of in-house tests as analyte specific reagents and set up a series of controls applicable to the manufacturers selling these devices and the laboratories using them.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

Questions and Answers

1. What is the definition of an analyte specific reagent?

FDA defines analyte specific reagents in 21 CFR 864.4020 as "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended to use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens." In simple terms an analyte specific reagent is the active ingredient of an in-house test.

2. How should one use an analyte specific reagent?

One should use an analyte specific reagent in conjunction with other general purpose reagents and general purpose instruments by a laboratory to set up an in-house ("home brew") test or laboratory testing service. While specimens can travel to the lab setting up this service, the test itself is not marketed outside of the single lab setting up this service. Analyte specific reagents should

have clear activity as the active ingredients of an in-house test but should be provided without instructions for use or performance characteristics. It is the responsibility of the laboratory using the ASR to develop a recipe for the test at hand and to take responsibility for establishing and maintaining performance.

3. What requirements does FDA place on the manufacturer of an ASR?

Manufacturers of ASRs must

- Register and list with FDA (21 CFR Part 807).
- Follow the quality system regulations (21 CFR Part 820).
- Label class I exempt ASRs as building blocks according to the language in 21 CFR 809.10(e)(1)(x) "Analyte Specific Reagent. Analytical and performance characteristics are not established."
- Restrict ASRs for sale to laboratories designated as high complexity under CLIA. These labs are thought to have the personnel and quality systems in place to allow for the development of in-house tests.

4. What requirements does FDA place on the laboratory using an ASR?

Laboratories using an ASR must

- Be certified as high complexity under CLIA.
- Establish and maintain the performance of the test under the requirements of CLIA.
- Label the test result to indicate its status as an in-house test in accordance with 21 CFR 809.30(e) as follows: "This test was developed and its performance characteristics determined by [Laboratory Name]. It has not been cleared or approved by the U. S. Food and Drug Administration." This statement would not be applicable or required when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR.

5. Can laboratories add additional labeling or use promotional material to clarify the status of their in-house assays?

Yes. Although not part of the rule, FDA has indicated that laboratories may add information in test reports or in promotional material to clarify that FDA is not requiring the in-house test to go through premarket FDA review.

6. Do CMS and other healthcare insurers reimburse laboratories for in-house tests?

Often. FDA premarket review does not take into account reimbursement issues. While FDA review may be one factor considered in reimbursement decisions, CMS and other healthcare insurers may choose to reimburse for in-house tests and in some cases may choose not to reimburse for tests found safe and effective by FDA.

7. What reporting requirements exist for ASRs?

Manufacturers and healthcare facilities must report deaths and serious injuries that an ASR has or may have caused or contributed to in accordance with 21 CFR Part 803. Individuals may also submit voluntary reports using the FDA MedWatch program, http://www.fda.gov/medwatch/ or call 1-800-FDA-1088.

8. Are there any exceptions to the ASR rule?

Yes. FDA has classified ASRs involved in blood screening under the ASR rule as either class III or in selected cases class II devices. ASRs used to diagnose life-threatening contagious diseases with high public health impact are also classified as class III products. Examples of these include tests for HIV and tuberculosis.

9. Who can I contact if I have questions about the ASR rule?

Contact Steven Gutman, M.D., at 301-594-3084, sig@cdrh.fda.gov, or by writing to the Food and Drug Administration, 2098 Gaither Road, HFZ-440, Rockville, MD 20852.