

FDA's Regulation of Analyte-Specific Reagents

Confusing and at times counterintuitive, the ASR rule applies to materials used in in-house-developed tests, not the assays themselves.

Jeffrey K. Shapiro and Randy J. Prebula

Hogan & Hartson LLP

One of the most confusing areas of FDA regulation surrounds the requirements governing analyte-specific reagents (ASRs). ASRs are raw materials and components used to develop laboratory assays. This article will provide a brief background on FDA's regulation of ASRs, summarizing the key ASR requirements and addressing some common misconceptions and pitfalls in this area.



Jeffrey K. Shapiro



Randy J. Prebula

Background

The story of FDA's ASR regulation begins with in-house-developed assays. On a daily basis, doctors send patient blood, urine, tissue, and oral specimens to laboratories for testing. The laboratories perform the requested assays and report the test results. Often, the labs use assays prepared by their staff members. These assays are typically referred to as *in-house-developed assays*, or, more colloquially, as *home brews*.

Despite the informal name, home-brew assays are widely accepted as scientifically valid and are relied upon routinely throughout the healthcare system. They are extensively regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement of 1988 (CLIA).

In August 1992, FDA issued a draft compliance policy guideline propos-

ing to apply general medical device regulation to home-brew assays. The laboratory community objected, arguing that they were adequately regulated under CLIA, that FDA regulation would be duplicative, and that FDA lacked legal authority to regulate laboratory testing services. FDA withdrew its proposal, but insisted that it had authority to regulate home brews should it wish to do so.

In November 1997, however, CDRH published a final rule governing the use of ASRs in certain in vitro diagnostic products (IVDs) and in-house laboratory assays. The final rule was the culmination of a lengthy process in which FDA sought to determine how, if at all, it would regulate clinical laboratories that prepare in-house assays using ingredients purchased from third-party biological and chemical suppliers.¹ In

the ASR regulation, FDA invoked the restricted-device authority in section 520(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). It did so to impose certain restrictions on the sale, distribution, and use of ASRs when used as ingredients of home-brew assays and in certain IVDs.

As FDA made clear, the agency was not actively regulating the in-house tests and had determined that strong public health reasons existed for continuing this approach.

In the final rule, FDA recognized that "the use of in-house-developed tests has contributed to enhanced standards of medical care in many circumstances, and that significant regulatory changes in this area could have negative effects on the public health." The agency said that the laboratories would be responsible for both the quality and interpretation of results generated from those tests.² Thus, the final rule focused not on the in-house tests, but on the ASRs that are used in preparing such tests.

Summary of the ASR Regulation

The regulation defines ASRs 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 for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.”³ This definition includes many different types of chemicals and biological components, such as mouse monoclonal antibodies to cancer markers, oligonucleotides that bind with DNA or RNA from infectious organisms or viruses, and chemicals that react with cholesterol or digestive enzymes. The key characteristic of each component is its ability to bind to or react with a

regardless of classification, all ASR manufacturers must comply with FDA’s postmarket requirements, including establishment registration, device listing, and compliance with FDA’s quality system regulation (QSR), medical device reporting (MDR) requirements, and ASR labeling and distribution requirements.⁵

To control the use of ASRs, FDA imposed a comprehensive set of restrictions. For example, ASRs may only be sold to: (1) diagnostic device manufacturers; (2) clinical laboratories that are CLIA qualified to perform

optimization of tests developed with the ASR beyond what we’ve already covered. It is also unlikely that FDA will permit ASR manufacturers to provide technical support for the ASR—beyond providing the identity and purity data. In fact, FDA has stated that provision of laboratory instructions on the use of an ASR would be viewed as “evidence that a kit or system is being marketed rather than used as an ASR or building block for an assay.”⁹

Similarly, providing ASR users with support, instrument setup, sample preparation, and data collection information exceeds FDA’s expectations. The agency has stated that “the responsibility for developing this information is clearly assigned to the laboratory, not the ASR manufacturer. The only responsibility the ASR manufacturer has is to produce product according to the quality system regulation, to label it clearly as a building block for use in ‘home-brew’ assays, and restrict sales to high-complexity laboratories.”¹⁰

The ASR requirements also extend to the clinical laboratories that purchase and use ASRs to develop home-brew tests. Specifically, laboratories that prepare in-house tests using an ASR purchased from a third-party supplier are required to append the following statement to the test report: “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 is not required when test results are generated using a test that was cleared or approved in conjunction with review of Class II or III ASRs, which require premarket clearance or approval.¹¹ The statement is also not required if all of the ASRs in the home brew are created in-house rather than purchased.¹²

Common Misconceptions and Pitfalls

Because the ASR regulation is so complex, misconceptions common. Three requirements are critical.

ASRs Cannot Be Sold as Test Kits. By definition, ASRs are a single component of a diagnostic test. Many IVD manufacturers, however, market so-

Manufacturers are not permitted to include in the ASR labeling or promotional materials any statement regarding analytical or clinical performance of the ASR.

substance whose detection and measurement is clinically meaningful.

Under this definition, ASRs are not diagnostic tests, nor are they combinations of reagents, controls, disposable labware, or instrumentation provided for the performance of diagnostic tests. Rather, an ASR is a single (albeit key) component in any diagnostic test manufactured anywhere in the world, including in clinical laboratories, IVD device manufacturing facilities, and forensic or research laboratories. However, ASRs are only subject to regulation as medical devices when they are purchased by clinical laboratories for use in home brews or certain IVD tests.

Most such ASRs are classified as Class I and exempt from the agency’s 510(k) premarket notification requirements. ASRs are classified in Class II or Class III when intended for use in blood banking, donor screening, and certain infectious disease testing. (FDA regulations for human blood and blood components require that tests used by establishments for these applications be approved by FDA. Accordingly, home-brew tests used in blood banking and donor screening require FDA clearance, approval, or licensure.⁴) Re-

high-complexity testing under 42 CFR Part 493, or clinical laboratories regulated under the Veteran’s Health Administration Directive 1106; or (3) organizations that use the reagents to make tests for forensic, academic, research, and other nonclinical (non-medical) uses.⁶ In addition, ASRs may be sold only for use in home-brew tests that are ordered on a prescription basis.

The ASR rule also comprehensively governs the information that manufacturers provide on the label or with the ASRs. For example, ASR manufacturers must provide specific information, including among several other items the proprietary name, common name, and quantity or concentration of the reagent; the source and a measure of its activity; and the name and place of business of the manufacturer.⁷

ASR manufacturers are not permitted to include in the ASR labeling or promotional materials any statement regarding analytical or clinical performance of the ASR.⁸ In our experience, FDA has interpreted this requirement to mean that ASR manufacturers are not permitted to provide information on assay methods or techniques, nor are they permitted to assist the laboratories with the

called ASR kits. These “kits” contain, in some instances, much more than a single component—such as an analyte-specific reagent coupled to a solid surface, positive and negative control solutions, instructions for conducting or validating specific test methods, and so on. Most likely, FDA would consider such kits to be finished IVD tests that require FDA clearance or approval.

ASRs Cannot Be Sold with Validation Information. Some companies run afoul of the ASR regulation by providing technical assistance and assay validation information to clinical laboratories. These companies argue that, as the reagent’s manufacturer, they are best suited to tell purchasers how the ASR should be used. FDA disagrees with this position, however. It believes that ASRs are merely ingredients of an assay, and that the test developer (i.e., the clinical laboratory) should fully control test development and validation. Any information provided by an ASR manufacturer to ensure that the final finished test performs appropriately likely will lead FDA to classify the company as a joint manufacturer of the diagnostic test.

Medical and Performance Claims Are Prohibited. Many ASR manufacturers make medical and assay performance claims. Under the ASR regulation, manufacturers may state that an ASR recognizes, binds to, or reacts with a specific analyte—Factor V Leiden RNA, Her-2/neu oncogenes, or cystic fibrosis genetic mutations, for example. They may not promote their reagents for applications such as the diagnosis of breast carcinoma, the determination of patients’ eligibility for drug treatment, or the identification of differences in metabolic activity as an aid in selecting specific drug therapies. Rather than promoting an ASR with a known specificity, manufacturers making such claims are promoting the use of the ASR to achieve a specific result.

Finally, we have seen some ASR manufacturers tout the ability of laboratories to use their ASRs in tests

that can “detect and quantitate” viruses, despite FDA’s specific prohibition on providing analytical or clinical performance statements for ASRs. These types of claims are prohibited under the ASR regulation.

Conclusion

It is not surprising that the ASR regulation has proven to be one of the least understood and most abused FDA regulations. It is confusing and has counterintuitive features. For example, under the FD&C Act, medical devices and their components typically are subject to the same level of regulation. Under the ASR regulation, however, FDA reg-

It is not surprising that the ASR regulation has proven to be one of the least understood and most abused of FDA regulations.

ulates only the ASR components and not the home-brew assay itself (except in a few specific cases). To add to the confusion, ASRs are only treated as medical devices when sold to particular customers (clinical laboratories) for a particular use (home-brew assays). Therefore, a manufacturer of ASRs may find itself regulated for interaction with some customers and not others.

From the standpoint of clinical laboratories, it is problematic that the use of an ASR purchased from a third-party supplier is the trigger for the disclaimer of FDA clearance or approval on the test report. In contrast, if the ASR is developed in-house, the disclaimer is not required. Thus, the same home-brew assay may or may not require a disclaimer based upon whether any of dozens of ingredients were purchased or developed in-house.

It is also illogical (and perhaps even misleading) for FDA to require a statement that an assay has not been cleared or approved when the agency itself does not require the assay to be cleared or approved. By classifying them as Class I, FDA exempted most ASRs from 510(k) clearance requirements and, in turn, decided not to regulate in-house tests that are prepared from

these ASRs. It makes little sense, then, to require clinical laboratories to warn physicians that the testing services were developed without FDA review. It would be more accurate to observe that the agency does not require such clearance or approval.

Ultimately, the ASR rule imperfections bear the hallmarks of a compromise. FDA felt a need to impose some level of regulation on home-brew assays, but settled for regulating some of their ingredients—at least for now. At best, the ASR rule may marginally improve the quality of some ingredients that clinical laboratories use in home-brew assays, albeit at the cost of significant ad-

ministrative complexity. More importantly, the ASR rule may only be the first step toward significant FDA regulation of home-

brew assays. For instance, FDA has recently made known its interest in regulating home-brew tests for genotypic analysis of certain retroviruses. Industry should be prepared in the coming years for a continued FDA involvement in regulating home-brew assays.

References

1. 61 *Federal Register*: 10484 (March 14, 1996).
2. 62 *Federal Register*: 62243, 26249 (November 21, 1997).
3. 21 *CFR* 864.4020(a).
4. 21 *CFR* 610.40(b).
5. 21 *CFR* 809.20.
6. 21 *CFR* 864.4020(a)(1) and (2).
7. 21 *CFR* 809.10(e)(1)(x) and (xi).
8. 21 *CFR* 809.30(d)(4).
9. Agency Information Collection Activities, 66 *Federal Register*: 1140 (2001).
10. Agency Information Collection Activities, 66 *Federal Register*: 1141 (2001).
11. 21 *CFR* 809.30(d)(3) & (e).
12. 62 *Federal Register*: 62249. ■

The author will be responding to questions and comments about this article in *MD&D*'s Author Forums through March 14, 2003. Visit www.devicelink.com/mddi and select the Author Forums link.