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AdvaMed

Advanced Medical Technology Association

September 16, 2005

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

Dear Sir or Madam:

The Advanced Medical Technology Association's (AdvaMed) Analyte Specific Reagent Working Group is pleased to submit the attached document "Most Frequently Asked Questions About Analyte Specific Reagents; Industry Proposal" to the docket for consideration by the Center for Devices and Radiological Health's Office of In Vitro Diagnostics Evaluation and Safety as a draft guidance document. We believe that the document will provide clarity for both the laboratory community and manufacturers in their understanding of the regulations and policy surrounding the manufacture, distribution and use of analyte specific reagents (ASRs).

AdvaMed has been involved in efforts to clarify the ASR rule since FDA issued the regulation in November of 1997. At that time we worked with the laboratory community to develop guidance that described how ASRs fit into the continuum of products offered by in vitro diagnostic manufacturers. Overtime, we have noted that further clarifications are needed regarding the roles of the laboratories and manufacturers as related to these products. This document attempts to provide those clarifications.

If you have any questions regarding the contents of the proposed guidance, please contact me.

Sincerely,

A handwritten signature in black ink that reads "Carolyn D. Jones". The signature is written in a cursive, flowing style.

Carolyn D. Jones
Associate Vice President
Technology & Regulatory Affairs

MOST FREQUENTLY ASKED QUESTIONS ABOUT ANALYTE SPECIFIC REAGENTS; INDUSTRY PROPOSAL

1. What are ASRs?

ASR stands for "Analyte Specific Reagent." ASRs are defined as "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acids sequences, and similar reagents which, through specific binding or chemical reactions 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." (21 CFR 864.4020(a)). ASRs are *in vitro* diagnostic devices that are regulated by FDA; subject to general controls, including the Quality System (GMP) Regulation, 21 CFR Part 820, as well as the specific provisions of the ASR regulation.

FDA classifies medical devices, diagnostics and ASRs into Class I, II, or III according to the level of regulatory control that is necessary to assure safety and effectiveness. These classifications also include consideration for the level of risk associated for diagnostic purposes. The classification of an ASR determines the appropriate premarket process and labeling requirements. Unlike the original classification process in the 1970's, where all known products were classified and subsequent unclassified products were automatically in Class III, ASRs are determined to be in Class I unless FDA proactively classifies specific products otherwise. This has been done, for example, for TB and HIV.

2. What is the ASR regulation?

FDA issued a regulation in November of 1997 classifying ASRs based on their risk to public health. The regulation allows certain reagents to be distributed to clinical laboratories for use in their own laboratory- developed ("home-brew") tests, without requiring the manufacturer to submit 510(k)s or PMAs for the majority of those reagents. This regulation went into effect on November 23, 1998. The ASR regulation affects not only manufacturers and distributors of reagent products, but also established specific requirements for results reported by laboratories and ordering physicians. (See 21 CFR 809.10(e), 809.30, and 864.4020)

3. What is a laboratory-developed (home brew) test?

A home-brew test is a test developed by a clinical laboratory intended for clinical or diagnostic purposes and may use a combination of one or more ASRs, general purpose laboratory reagents, general laboratory instruments, and/or instrumentation with *bona fide* user definable, open capabilities.

While this document cannot list specific instruments by name, the intent is for the reader to understand that the laboratory developing the test must be able to independently determine positive, negative, or equivocal results (when appropriate) and set their own cut-offs. In some cases, the user may also desire to set incubation times or temperatures. In summary, laboratory-developed tests must be designed, formulated, and sufficiently validated by the clinical laboratory using the test (without test development assistance directly from the manufacturer), before clinical results are reported.

4. How are ASRs different from General Purpose reagents?

General Purpose Reagents (GPRs) are those chemical reagents that have general laboratory application and are not labeled for a specific clinical or diagnostic use. They are not analyte-specific and may be combined with or used in conjunction with one or more ASRs. (See 21 CFR 864.4010(a)) ASRs are reagents composed of specific chemical components, probes or antibodies specific for a chemical substance or ligand (see FAQ 1 above) that are considered the "active ingredients" or "building blocks" of laboratory tests.

5. How is the ASR regulation related to in vitro diagnostic products labeled for research or investigational use?

Products labeled as research use only (RUO) or investigational use only (IUO) are test kits or reagents in different stages of development.

- RUO products are in the early phase of development, that is, either basic research or the initial search for potential clinical utility, and cannot be commercialized by any manufacturer for human clinical diagnostic use. During this phase, the focus of manufacturer-initiated studies is typically to evaluate limited-scale performance and potential clinical or informational usefulness of the test. These products are labeled "*For Research Use Only. Not for use in diagnostic procedures.*" as required under 21 CFR 809.10 (c)(2)(i).
- IUO products are test kits/systems in the clinical investigation phase of development, and cannot be commercialized by the manufacturer. The test cannot be used for human clinical diagnosis without confirmation of the diagnosis by another cleared or approved test or procedure (21 CFR 812.2(c)(3)(iv)). During this phase, the safety and effectiveness of the product are being studied; i.e.; the clinical performance characteristics and expected values are being determined in the intended patient population(s). These products must be labeled "For Investigational Use Only. The performance characteristics of this product have not been established." The specific labeling for these types of products is found in 21 CFR 809.10(c)(2)(ii).

ASRs, conversely, are reagents, such as antibodies or probes, as defined by 21 CFR 864.4020 which can be used by a laboratory to develop tests for specific analytes (see FAQ 1). The results generated using these laboratory-developed tests are intended for diagnostic use by the ordering physician. The specific labeling requirements for the manufacturer of the ASR are found in 21 CFR 809.10 (e) and the restrictions for sale, distribution and use applicable to both the manufacturer and the reporting laboratory are found in 21 CFR 809.30.

6. What is the difference between an ASR and a RUO reagent?

An ASR is manufactured using good manufacturing practices (GMP) of the Quality Systems Regulations, and can be used in clinical diagnostic assays, the results from which can be used in patient care. Because there is no requirement to manufacture RUO reagents under GMP, assays using these reagents may not provide reproducible results. RUO reagents and product labeled as such should not be used in clinical diagnostic assays (21 CFR 809.10(c)(2)(i)).

7. What was the reason for this regulation?

FDA developed the ASR rule to clarify FDA policy with regard to the status of laboratory-developed 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 laboratory-developed tests as analyte specific reagents and set up a series of controls applicable to the manufacturers selling these reagents for clinical diagnostic use.

FDA regards regulating ASRs using general controls and exempting them from premarket notification requirements as the least burdensome approach. This approach relies on the cGMPs (the Quality System regulation at 21 CFR 820), medical device reporting, the Clinical Laboratory Improvement Amendments (CLIA) and labeling requirements to adequately control these products.

8. What does the ASR regulation require?

The regulation states that since November of 1998, manufacturers must register with the FDA and file an ASR device listing as required for any other medical device. Device listing names can be found in a document available from FDA entitled "Classification Names for Medical Devices and In Vitro Diagnostic Products" (FDA 95-4246). For those that do not have a published "classification name," that section of the device listing simply reads "ASR."

The regulation also stipulates a labeling statement that must appear on the product container and the limitations and requirements of package insert labeling. The regulation requires manufacturers of ASRs to comply with cGMPs for medical devices.

For laboratories that purchase ASRs for laboratory-developed tests, a specific statement must be printed on the laboratory test reports generated using these test reagents. This statement must indicate that the reagent and the test used to produce the results have not been subject to a premarket review by FDA and that the performance characteristics of the test have been established by the laboratory (21 CFR 809.30(e)).

The rule also requires that the ordering of these tests be limited to physicians and others licensed by applicable state law to order such tests (21 CFR 809.30(f)).

9. To whom can ASRs be sold?

ASRs may only be sold to:

- (1) In vitro diagnostic manufacturers;
- (2) Clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity testing or clinical laboratories regulated under VHA Directive 1106, and
- (3) Organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners, e.g., forensic, academic, research and other non-clinical laboratories. (21 CFR 809.30)

10. When do I have to comply?

The regulation has been in place since 1998. Compliance with the regulation is required for both manufacturers and laboratories.

11. What do I have to do to meet the requirements to manufacture, sell, distribute, or use ASRs?

As an ASR Manufacturer, you must register your firm with FDA, list your products with the standard FDA device listing form, manufacture according to cGMP, only sell to those entities listed in 21 CFR 809.30(b), and report adverse events under the MDR rule. Written materials associated with ASRs shall not include any claims for clinical utility or include any specific clinical performance characteristics or instructions for use. However, scientific information may be included on chemical/molecular composition, nucleic acid sequence, binding affinity, cross-reactivities, known mutations associated with the sequence, and interaction with substances of known clinical significance. Reference information, such as peer-reviewed publications, in response to unsolicited requests for peer-reviewed scientific literature describing research studies performed utilizing an ASR can also be provided (See FAQ 36). Class I ASRs must be labeled as "Analyte Specific Reagent. Analytical and performance characteristics are not established" (21 CFR 809.10 (e)(1)(x)). Class II and III ASRs must be labeled as "Analyte Specific Reagent. Except as a component of the approved/cleared test (name of approved/cleared test) analytical and performance characteristics are not established" (21 CFR 809.10 (e)(1)(xi)).

As a Distributor, you must record complaints. No claims of clinical utility can be made for an ASR, nor can clinical performance characteristics be provided. Only the product descriptions may be included to describe the product as listed above.

As a Laboratory Director, your laboratory must be governed under CLIA or comparable regulations and you must be registered as a high complexity laboratory to purchase and use these reagents to develop and perform laboratory-developed tests for clinical use. When you use an ASR as a component of a laboratory-developed test, you must inform the person ordering the test that the test was developed, and the performance characteristics established by the laboratory, without FDA review by adding the disclaimer found in 21 CFR 809.30(e) to the test report.

12. Can ASRs be used for research?

ASRs can be used for research applications. The ASR requirements, including the need for the laboratory report disclaimer, apply only to diagnostic use of these products and not to research applications.

13. Can ASRs be purchased from any supplier?

Yes, provided the products are listed with the FDA, are manufactured in compliance with cGMP requirements, and meet the labeling requirements of the regulation.

14. Can ASRs and sufficient GPRs used by a laboratory to develop a test be purchased from a single manufacturer or distributor?

Yes, provided all the ASR and GPR requirements are met. ASRs, meeting the definition in 21 CFR 864.4020, are "building blocks" and as such, should not be promoted or sold by manufacturers in kit configurations; therefore the expectation by laboratories should be that ASRs and GPRs will not be packaged in the traditional assay kit manner.

In many cases, a GPR will be suitable for use with several different ASRs. Although a GPR may consist of a single substance or formulation of multiple substances as defined by 21 CFR 864.4010, they should typically be widely acknowledged and readily available for use with a particular basic technology. Accordingly, GPRs should not be promoted as part of, or

for use with, a particular ASR that otherwise could be construed as a kit. In that respect, selection, determination of proper quantities, and use of GPRs with a given ASR or combination of ASRs is the responsibility of the end-user.

15. Can a manufacturer or distributor tell a laboratory which ASRs are useful for a particular application, for example which monoclonal antibodies or probes are useful for leukemia or lymphoma testing?

ASR labeling may indicate the affinity of the reagent, such as "chronic myelogenous leukemia antibody" or "chronic myelogenous leukemia nucleic acid probes." Other similar information, such as the affinity, target, or sequence of a DNA probe or a protein sequence, may also be provided. Manufacturers and distributors cannot make claims to physicians or laboratories of clinical uses or performance. They can, however, respond to unsolicited requests for information from the laboratorians or physicians for peer-reviewed publications using specific ASRs. In addition, manufacturers should take care to avoid overly descriptive names for their ASR that imply an intended use.

16. Am I going to be asked to sign anything when I purchase an ASR?

The ASR regulation does not require that the ASR manufacturer obtain any kind of certification from the laboratory, although some companies may voluntarily have such a program. However, the laboratory must be qualified under CLIA to perform high complexity testing or regulated under VHA Directive 1106.

17. Who determines which products are sold as ASRs?

The manufacturer determines which products are sold as ASRs. Contact the manufacturer if you have questions regarding the availability of ASRs. Manufacturers are encouraged to consult with the FDA regarding the classification of the ASR.

18. What if no one manufactures an ASR for a test I wish to develop in my laboratory?

You can request that the manufacturer of a reagent meet the regulatory requirements and label that particular product as an ASR. If the manufacturer does not choose to label the product as an ASR, the laboratory could develop its own reagent and, provided the reagent is not sold or distributed to other clinical or research laboratories, that reagent would not be subject to the ASR labeling requirements.

19. When an ASR is sold by one IVD manufacturer to another IVD manufacturer, what distinguishes that ASR from being a "component"?

An ASR that is sold to a manufacturer is a component when the purchasing manufacturer uses the reagent as part of a medical device.

20. What disclaimer statement is required when using an ASR in a laboratory-developed test?

The laboratory that develops a laboratory-developed test using a Class I ASR must 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" (21 CFR 809.30(e))."

21. Is the ASR disclaimer statement required for all laboratory-developed or modified tests?

If the laboratory does not purchase the ASR from a manufacturer but makes its own, and all activities in support of production of the active ingredients occur within the laboratory, the ASR disclaimer statement is not required on the resulting test report, although FDA has asked laboratories to consider such a disclaimer in the interest of fair disclosure.

22. Are laboratories required to issue ASR disclaimers on test reports when a test is being used by a laboratory for a non-approved FDA use?

No. The ASR disclaimer statement is intended to cover laboratory-developed tests using ASRs and performed for clinical or diagnostic use. It is not intended to cover "off-label" uses of FDA-cleared or approved products (e.g., use of an FDA-cleared or approved product for a use other than that designated on the label).

23. Is the disclaimer language required on test reports if a laboratory modifies an ASR?

Yes. The disclaimer statement is required in all instances where an ASR is used by a laboratory in a laboratory developed test.

24. Is a disclaimer statement necessary when using an assay purchased from the manufacturer labeled as an immunohistochemistry (IHC) reagent?¹

No. Most assays purchased from manufacturers under the IHC label are marked as IVD rather than ASR and do not require a disclaimer statement when used by laboratories. The disclaimer statement applies only to ASRs.

25. Is a disclaimer statement required when ASRs are used in non-clinical laboratory settings for purposes other than providing clinical or diagnostic information to patients and practitioners (e.g., forensic, academic, research settings)?

No. The ASR rule does not apply to reagents sold to and used in non-clinical settings.

26. Is a disclaimer statement necessary when a laboratory uses an ASR that is FDA-approved or cleared as part of a test kit and provided to the laboratory independent of the approved or cleared test kit?

Yes, if the manufacturer distributes an FDA-cleared or approved test kit component as an ASR independent of the test kit. A disclaimer statement must be appended to the test report when an ASR is used independently of the FDA-approved or cleared test kit.

27. May a laboratory add language to the prescribed disclaimer statement clarifying that FDA clearance or approval of the test is not required, and the test should not be regarded as investigational or research?

Yes, as long as the FDA prescribed language is also contained in the disclaimer.

28. What instrumentation meets the requirements for use with an ASR?

Any general purpose laboratory instrument (such as spectrophotometer, HPLC, or flow cytometer) can be used with laboratory-developed tests using ASRs. In addition instruments produced by ASR manufacturers can be used, provided the laboratory

¹ Most immunohistochemical stains (IHCs) do not fall under this regulation. FDA reclassified such stains as Class I, exempt from 510(k) submissions, so IHCs carry an "IVD" label rather than an ASR label.

determines the appropriate reference ranges, assay cut-off values for positive or negative results for qualitative tests, and other performance characteristics and interpretation criteria for the test. Automated instruments that use a standardized process may also be configured with GPRs and ASRs, provided they have user-defined capabilities, which allow the user to define, optimize, and validate the test performance characteristics and interpretation criteria. Manufacturers cannot sell ASRs as part of a system that does not have user-defined capabilities. That is, the instrumentation should be able to run different ASRs, allows parameter modification, or that has a user interface that the laboratory can modify to define specific parameters for their laboratory-developed assay. If instrumentation is used, it is the laboratory's responsibility to select instrumentation and validate the performance of the laboratory-developed assay on that instrument.

29. **Can General Purpose instrumentation be combined (for example, combining an automated extraction instrument with a spectrophotometer)?**

Yes, but it is the responsibility of the laboratory to select and validate instrumentation linkages that would constitute a system. Manufacturers are restricted from offering system solutions specifically for their particular ASRs.

30. **What software meets the requirements for use with an ASR?**

Any software that allows user-defined capabilities, for example, setting a cut-off value, or setting incubation or reaction times, can be used with instrumentation to run laboratory-developed tests using ASRs. General purpose "off-the-shelf" laboratory software such as Microsoft® Excel® spreadsheets or macros created for result determination may also be used. The laboratory is expected to verify or validate such software output. The manufacturer of the ASR, however, is restricted from defining the specific assay cut-offs for use by the software.

31. **How should the laboratory validate a test that is developed with an ASR?**

Appropriate validation is required under CLIA for any laboratory that creates a new test or modifies an existing assay, as defined under 42 CFR §493.1253(b)(2). Since validation consists of many steps and many parameters and the CLIA regulations are somewhat silent on defining the appropriate amount of validation required for tests of varying levels of potential public health risk, it is the responsibility of the user to determine appropriate validation when planning to put an ASR-containing laboratory-developed test into use. Given the availability of many Clinical Laboratory Standards Institute (formerly "NCCLS") and ISO standard documents, and public information describing validation studies required of IVD manufacturers, the expectation is that the level of validation undertaken for laboratory-developed tests using ASRs should be consistent with that necessary for any laboratory-developed diagnostic test.

32. **Can the manufacturer help with the validation of a test that contains an ASR?**

The laboratory is required to conduct validation under the CLIA regulations. This CLIA validation by the laboratory is the minimum required for the laboratory to generate clinical results (41 CFR 493.1253). Manufacturers should not assist with the validation of a laboratory-developed test using a specific ASR. However, the manufacturer may have knowledge of generally accepted practices that can assist the laboratory in determining appropriate validation elements and the level of validation required, consistent with the expectation stated in FAQ#31. The latter may be provided in response to an unsolicited request from the end-user; however, such assistance should be general in nature and not specific to validation of a given ASR for a particular clinical use.

33. How should a laboratory obtain information regarding protocols or how to perform an assay?

ASRs are intended to be a component of an assay developed and validated by the user. As such, the manufacturer should not supply a product-specific protocol for use of the ASR. Information on general assay procedures for an assay type may be part of the instructions, but it may not contain clinical utility data or assay cut-off information.

Protocols and performance characteristic expectations may be obtained from other laboratories performing or developing the same test, through peer-reviewed literature or from internal laboratory experience gained from developing similar assays.

34. What quality control reagents can be used for laboratory-developed tests?

The laboratory is responsible for determining what kind of quality control is appropriate for a laboratory-developed test, and what quality control reagents are required. In some cases, such as a characterized analyte (e.g., PSA), commercially-available quality control materials may be available. In other situations, the laboratory may create their own quality control material from characterized patient samples, transcripts or other material. Quality control requirements for high complexity tests are also described in the CLIA laboratory regulations (42 CFR 493.1255).

35. What kind of quality control (materials/reagents) can a manufacturer supply?

Purchasing and availability of quality control materials is independent of the purchase of an ASR. Information may be obtained through peer-reviewed literature, communications with other laboratories who have worked with the ASR, or by specific request to the manufacturer.

36. Where can a laboratory obtain information about a particular ASR?

Information may be obtained through peer-reviewed literature and communications with other laboratories who have worked with the ASR. Information may also be obtained by specific request to the manufacturer for peer-reviewed and published/presented literature. Although some of the literature may include results from clinical studies, the details of a manufacturer's response to the request, should not include information regarding clinical utility, clinical performance, specific instructions-for-use (IFU), and/or specific validation protocols. As indicated by the Rule, information provided by the manufacturer should be limited to characteristics of the ASR ("building block") itself and not its use as part of a test and/or test system.

37. Are some ASRs Class II or Class III, requiring a premarket submission?

Yes, certain ASRs are subject to FDA premarket submission, such as the analytes used for assessment of the blood supply (e.g. HIV testing of blood products) or used for the diagnosis of a contagious condition that is highly likely to result in a fatal outcome with high public health impact (such as tuberculosis.)

38. Do some Class I ASRs require a premarket submission?

Currently all Class I ASRs are exempt from premarket submission. However, under section 510(l) of the Act (21 U.S.C. §360(l)), FDA may reclassify a Class I exempt device and require premarket notification. FDA has stated that they reserve the right for such reclassification in cases where FDA determines the ASR is "intended for a use which is of substantial importance in preventing impairment of human health" or if it "presents a potential unreasonable risk of illness or injury." If 21 CFR 864.9 applies to ASRs, "The

exemption from the requirement of premarket notification for a generic type of class I or II device is only to the extent that the device has existing or reasonably foreseeable characteristics of commercially distributed devices within that generic type.²

39. **Who makes the initial risk determination when classifying ASRs?**
Manufacturers make the initial determination using references available from the FDA. However, if FDA does not agree, FDA makes the final determination. Manufacturers should review the characteristics and classification of other similar ASRs or IVDs to determine the applicability and fully understand potential risk as it relates to proper classification of the device.
40. **Where can I obtain additional information on the FDA ASR and IHC rules?**
Additional information can be obtained by contacting the College of American Pathologists (CAP) Division of Government and Professional Affairs, 800 - 392 - 9994, ext. 119, and asking for the "Analyte Specific Reagent" information package or the "Immunohistochemistry (IHC)" information package. Companies that manufacture and/or distribute ASRs may also be able to answer your questions. You may also contact FDA. The appropriate contact is the Director, Office for In Vitro Diagnostics Evaluation and Safety (OIVD), at 240- 276-0484, or CDRH's Division of Small Manufacturers Assistance at 301-443-6597 or 1-800 - 638 -2041.

² It is not clear that 21 CFR 864.9 applies to ASRs. Section 864.9(c) has limitations specific to *in vitro* devices that directly contradict the stated scope of the ASR regulation.

In any case, if 21 CFR 864.9 does not apply to ASRs, FDA can require premarket submission through notice and comment rulemaking.