Guidance for Industry and FDA Staff
Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions

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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

Center for Biologic Evaluation and Research

GRZAN

Preface

Comments

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

INTRODUCTION

This guidance document is intended to clarify the regulations regarding commercially distributed analyte specific reagents (ASRs) (21 CFR 809.10(e), 809.30, and 864.4020), and the role and responsibilities of ASR manufacturers. This document is not intended to provide guidance on the role of clinical laboratories in the development of laboratory developed tests (LDTs). The guidance follows the substance, spirit, and meaning of the ASR regulations already in place.

The guidance addresses some frequently asked questions about how ASRs may be marketed, and provides FDA's Office of In Vitro Diagnostic Device Evaluation and Safety's (OIVD's) and the Center for Biologics Evaluation and Research's (CBER's) responses to those questions. Except where otherwise indicated, the use of the term "ASR" in this guidance document refers to commercially distributed ASRs and the term "manufacturer" refers to manufacturers of commercially distributed ASRs.

FDA is providing this guidance in order to eliminate confusion regarding particular marketing practices among ASR manufacturers. As noted in this guidance document, ASRs are building blocks of LDTs. (See section II of this guidance.) ASRs are defined and classified in a rule codified at 21 CFR 864.4020. With this guidance document, FDA seeks to advise ASR manufacturers that it views the following practices as being inconsistent with the marketing of an ASR, as defined under 21 CFR 864.4020:

- Combining, or promoting for use, a single ASR with another product such as other ASRs, general purpose reagents, controls, designated laboratory instrument(s), software, etc.
- Promoting an ASR with specific analytical or clinical performance claims,

instructions for use in a particular test, or instructions for validation of a specific test using the ASR.

Some manufacturers have believed that when they combine a Class I ASR, which is exempt from premarket notification requirements under section 510(l) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 360(l), with other products, or with instructions for use in a specific test, the product remains exempt because of the presence of an ASR. However, as explained in this guidance, when an ASR is marketed in the ways described above, FDA views the product as no longer being an ASR within the meaning of 21 CFR 860.4020 and instead views it as another type of in vitro diagnostic device (IVD) or device component not covered by the ASR regulations and, therefore, not necessarily exempt from premarket notification.

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.

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 follow the statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to 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 document, “A Suggested Approach to Resolving Least Burdensome Issues.” It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

FREQUENTLY ASKED QUESTIONS

I. The ASR Rule

1. What is the definition of an ASR?

ASRs are defined as “antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid 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 medical

devices that are regulated by FDA. They are subject to general controls, including current Good Manufacturing Practices (cGMPs), 21 CFR Part 820, as well as the specific provisions of the ASR regulations (21 CFR 809.10(e), 809.30, 864.4020).

2. What is the ASR rule?

This guidance document refers to three regulations as "the ASR rule." Published in 1997, the regulations define and classify ASRs (21 CFR 864.4020), impose restrictions on the sale, distribution, and use of ASRs (21 CFR 809.30), and establish requirements for ASR labeling (21 CFR 809.10(e)).

3. What was the objective of the ASR rule?

The ASR rule was designed to accomplish several policy objectives. One of the primary goals of the rule was to ensure the quality of the primary, active reagents of finished IVDs or LDTs. Another focus of the rule is the requirement for appropriate labeling to be appended to test results when ASRs are used by clinical laboratories in LDTs, so that healthcare users can understand when tests are being developed and validated by the laboratory and have not undergone FDA clearance or approval. 62 FR 62244. FDA adopted the approach of regulating most ASRs by means of general controls and exempting them from premarket notification requirements as the least burdensome approach. This approach relies primarily on cGMPs, medical device reporting, and labeling requirements to adequately control the risks associated with these devices. In addition, laboratories that develop tests using ASRs must be in compliance with the Clinical Laboratory Improvement Amendments (CLIA), 42 U.S.C. 263a 62 FR 62252.

4. What does the ASR rule require?

The rule classifies most ASRs as Class I devices subject to general controls under section 513(a)(1)(A) of the Act, but exempt from premarket notification. The general controls require ASR manufacturers to register and list their devices, 21 CFR 807.20(a), submit medical device reports (21 CFR Part 803), follow labeling requirements, 21 CFR 809.10(e), and follow cGMPs, 21 CFR 809.20(b). The rule also restricts the sale, use, distribution, labeling, advertising and promotion of ASRs. 21 CFR 809.30. One of these restrictions allows only physicians and other persons authorized by applicable State law to order LDTs that are developed using ASRs. 21 CFR 809.30(f). Another restriction requires the laboratory that develops an LDT using an ASR to add a statement disclosing that the laboratory developed the test and it has not been cleared or approved by FDA when reporting the test result to the practitioner. 21 CFR 809.30(e).

The restrictions also prohibit advertising and promotional materials for ASRs from making any claims for clinical or analytical performance. 21 CFR 809.30(d)(4). Consistent with this restriction, the labeling for Class I, exempt ASRs must bear the statement, "Analyte Specific Reagent. Analytical and performance characteristics are not established." 21 CFR 809.10(e)(1)(x). Manufacturers who wish to make

analytical and/or clinical performance claims for a product should submit an application to FDA for premarket review rather than marketing the product as an ASR. For example, performance claims might include statements such as, "This ASR can be used for quantification of [an analyte] to determine [a diagnosis]".

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

Yes. Although most ASRs are Class I, there are some ASRs that are Class II and Class III and that must be cleared or approved by FDA before they can be marketed in the United States. 21 CFR 864.4020. FDA classifies medical devices, including diagnostic devices such as ASRs, into Class I, II, or III according to the level of regulatory control that is necessary to provide a reasonable assurance of safety and effectiveness. These classifications include consideration of the level of risk associated with the device. 21 U.S.C. 360c. The classification of an ASR determines the appropriate premarket process.

An ASR is a Class II device if the reagent is used as a component in a blood banking test of a type that has been classified as a Class II device (e.g., certain cytomegalovirus serological and treponema pallidum nontreponemal test reagents). 21 CFR 864.4020(b)(2).

An ASR is a Class III device if the reagent is intended as a component in tests intended either:

- to diagnose a contagious condition that is highly likely to result in a fatal outcome and prompt, accurate diagnosis offers the opportunity to mitigate the public health impact of the condition (e.g., human immunodeficiency virus (HIV/AIDS) or tuberculosis (TB)); or
- for use in donor screening for conditions for which FDA has recommended or required testing in order to safeguard the blood supply or establish the safe use of blood and blood products (e.g., tests for hepatitis or for identifying blood groups). 21 CFR 864.4020(b)(3).

FDA considers ASRs intended to be used as a component in tests for diagnosis of HIV (including monitoring for viral load or HIV drug resistance mutations) to be Class III ASRs.

6. How does a manufacturer know whether its device is an ASR?

We recommend that ASR manufacturers consult this document for guidance on whether their product is or is not within the scope of the ASR rule. Manufacturers should contact FDA if they are unsure about the classification of their device to discuss any applicable regulatory requirements. Manufacturers who wish to obtain FDA advice on this matter in advance of marketing may consult with OIVD, or, with CBER for questions about HIV ASRs or ASRs for blood or cellular and tissue products.

II. What Meets the ASR Definition?

There has been some confusion about which products fall within and outside the definition of an ASR. Some of this confusion relates to a misunderstanding that a product is an ASR if it is labeled as one, even if the product contains analytical or clinical performance claims and does not meet the definition of an ASR.

In the preamble to the ASR rule, FDA stated that ASRs are the "active ingredients" of tests that are used to identify one specific disease or condition. ASRs are purchased by manufacturers who use them as components of tests that are cleared or approved by FDA and also by clinical laboratories that use the ASRs to develop LDTs used exclusively by that laboratory. 62 FR 62243, 62244. This is in contrast to what the preamble referred to as a "kit or system for 'in vitro diagnostic use'" that has a proposed intended use, indications for use, instructions for use, and performance characteristics. 62 FR 62243, 62250.

The ASR rule was intended to require that ASR manufacturers take certain actions, such as following cGMPs, to help ensure the quality of these reagents so that IVD manufacturers and laboratories who purchase them can produce tests that are safe and effective. A premise underlying the rule, however, is that laboratories and IVD manufacturers, rather than ASR manufacturers, design and develop the test in which the ASR is used, using their judgment and knowledge, and provide all necessary verification and validation.

Based upon this description, together with the ASR definition, FDA views an ASR as having the following characteristics:

- used to detect a single ligand or target (e.g., protein, single nucleotide change, epitope);
- not labeled with instructions for use or performance claims; and
- not promoted for use on specific designated instruments or in specific tests.

7. What are some examples of entities that FDA considers to be ASRs?

Examples of entities that are ASRs include:

- a single antibody (e.g., an anti-troponin I polyclonal or monoclonal antibody, whether untagged or tagged, e.g., conjugated to horseradish peroxidase),
- a single forward/reverse oligonucleotide primer[1] pair (e.g., a primer pair for amplification of a single amplicon, such as for amplification of the ΔF508 locus of the gene encoding the cystic fibrosis transmembrane regulator (CFTR)), or single forward or reverse primer individually,

[1] For the purposes of this guidance, a primer is defined as a nucleic acid sequence that is intended to initiate amplification by binding selectively to a complementary sequence in a large nucleic acid polymer.

- a nucleic acid probe[2] (whether untagged or tagged, e.g., conjugated to biotin or Cy™3) intended to bind a single complementary amplified or unamplified nucleic acid sequence,
- a single purified protein or peptide (e.g., purified B-type natriuretic peptide).

The above-listed examples would not be considered ASRs if they are marketed with clinical or analytical performance claims (e.g., quantification of an infectious agent, assessment of cardiac risk).

In addition to the examples listed here, there may be other products that can be appropriately marketed as ASRs provided they meet the criteria listed above, i.e., the ASR is used to detect a single ligand or target (e.g., protein, single nucleotide change, epitope), is not labeled with instructions for use or performance claims, and is not promoted for use on specific designated instruments or in specific tests. In the future, with the development of novel technologies, there may be products that meet the definition of an ASR (21 CFR 864.4020) that are dissimilar to the examples listed above. In those cases, ASR manufacturers should contact FDA with questions about specific products.

8. What are some examples of entities that FDA does not consider to be ASRs?

- Multiple individual ASRs (e.g., antibodies, probes, primer pairs) bundled together in a single pre-configured or optimized mixture so that they must be used together in the resulting LDT. For example, a set of 5 primer pairs combined in a single tube that are used to detect 5 different viral genotypes requires that all of these pairs be used together, and that they work together to accurately detect all five genotypes. This is an analytical claim for the product, and FDA does not consider this type of product to be an ASR.
- Products that include or require more than a single ASR (i.e., the product includes some or all of the products needed to conduct a particular test such as more than one ASR, general reagents, controls, equipment, software, etc.) and/or has instructions for use. FDA does not consider such a product to be an ASR but rather an IVD or IVD component not covered by the ASR rule.
- Reagents that are designed to require use in a specific assay or on a designated instrument (e.g., arrayed on beads). The requirement for reagents and designated instruments to be used together constitutes a performance claim that they will work properly when used in combination, since those specific reagents are intended for use with that specific instrument. FDA does not consider such a product to be an ASR but rather an IVD or IVD component not covered by the ASR rule.

When manufacturers have assembled ingredients towards the development of a test, such as in the examples listed above, the product is no longer an ASR. A

[2] For the purposes of this guidance, a probe is defined as a molecule that is intended to isolate, bind, or identify a specific target or ligand.

laboratory cannot validate that the way those individual ASRs and other components are combined by the manufacturer (e.g., the identity, concentration, purity) is appropriate for meeting the intended use and specifications of their in-house test. However, laboratories themselves are not precluded by the ASR rule from selecting and combining individual ASRs and other components in the development of their own in-house tests.

Other types of devices that do not meet the definition of an ASR include:

- Control material or calibrators.
- Products that have specific performance claims, or procedural instructions, or interpretations for use.
- Reagents offered with software for interpretation of results.
- Software for interpretation of assay results.
- Microarrays.

Manufacturers who wish to market a product in a fashion that is similar to the examples listed above should discuss the classification of their product with FDA prior to marketing.

9. How do General Purpose Reagents compare to ASRs?

A General Purpose Reagent (GPR) is "a chemical reagent that has general laboratory application, that is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and that is not labeled or otherwise intended for a specific diagnostic application." 21 CFR 864.4010(a). Like ASRs, GPRs are not labeled for a specific clinical or diagnostic use. Because GPRs are not analyte-specific, they should have the potential to be combined with, or used in conjunction with more than one type of ASR by the laboratory or IVD manufacturer that develops the finished test. In contrast, as stated above, an ASR is a specific chemical component, probe, or antibody that by its design determines which individual chemical substance or ligand can be detected.

III. Manufacturer Marketing Practices

10. To whom can manufacturers sell ASRs?

ASRs may only be sold to:

- in vitro diagnostic manufacturers;
- 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
- 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 nonclinical laboratories. 21 CFR 809.30 (b).

11. Can a manufacturer or distributor promote specific ASRs and GPRs for use together in developing a test?

No. As explained above, ASRs are considered specific individual "building blocks" of LDTs and finished IVDs tests, while GPRs are not intended for any specific diagnostic application. 21 CFR 864.4010, 864.4020. A product that is promoted for use with an ASR is intended for a specific diagnostic use with that ASR and therefore would not meet the GPR definition of being for "general laboratory application." Similarly, a product that is promoted for use with a specific GPR is intended for a particular intended use rather than as an ASR, which is a building block of LDTs. Therefore, a manufacturer who wishes to market its products as GPRs or ASRs should not promote or sell them together, including in finished or partial IVD test configurations.

We recommend that manufacturers who wish to market multiple different products as ASRs, e.g. multiple ASR primer sets to amplify different mutation loci in a single gene, rather than as IVDs or IVD components, avoid marketing the ASRs in a manner that suggests that use of particular ASRs together will provide a particular effect, or that these devices should be used together for a specific purpose.

12. Can the manufacturer include instructions with an ASR?

ASR manufacturers should not provide instructions for developing or performing an assay with an ASR. As explained above, FDA does not view reagents that are sold with instructions for developing or performing a test as ASRs because ASRs are intended to be building blocks for tests and are intended to be used to develop a test for which the developer must establish instructions for use and performance claims. 21 CFR 809.10(e)(1)(x), 809.30(d)(4). Instructions for use of an ASR in a particular test would constitute a claim that, when used as directed, the ASR will perform to detect a particular chemical substance or ligand.

On the other hand, instructions for proper storage and handling of an ASR must be provided. 21 CFR 809.10(e)(1)(vi). In addition, scientific information may be included on chemical/molecular composition, concentration or mass, nucleic acid sequence, binding affinity, cross-reactivities, known mutations associated with the sequence, and interaction with substances of known clinical significance. 21 CFR 809.10(e)(1)(iv).

13. 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 manufacturers and distributors should not make claims to physicians or laboratories regarding analytical or clinical performance for ASRs. The laboratories, not the ASR

manufacturers or distributors, are responsible for the design and performance of the test. 21 CFR 809.30(d)(4).

ASR labeling may indicate the affinity of the reagent, such as "anti-estrogen receptor antibody" or "ΔF508 CFTR nucleic acid probe." Other similar information, such as the affinity, target, or sequence of a DNA probe or a protein sequence, may also be provided because it describes the ligand to which the ASR is specific but does not claim to produce a particular clinical or analytical result. But a name such as "Cardiac Risk ASR" describes a specific clinical use for the product and FDA, therefore, would not consider such a product to be an ASR.

14. Can an ASR manufacturer supply quality control materials/reagents that can be used with an ASR?

Yes, but these materials should be promoted independently of specific ASRs. Marketing such materials for use with an ASR would indicate that the ASR manufacturer is actually marketing a product which could trigger premarket review requirements. Quality control materials should be promoted and sold using existing FDA classifications for quality control material (e.g., 21 CFR 862.1660, 862.3280, 864.8625).

15. Can a manufacturer or distributor market software for use with an ASR?

If an ASR manufacturer chooses to market software for use with its product, then the products together would not be considered an ASR. Software does not meet the definition of an ASR. FDA views marketing practices that directly suggest or state that particular software is needed to achieve a function of an ASR to cause the ASR part of the combination to fall outside of the ASR definition because the ASR would now be intended for use with the software. As a result, FDA's view is that ASR manufacturers should not promote, sell, or otherwise distribute software for use with a particular ASR.

16. What types of instrumentation can manufacturers promote for use with LDTs?

ASRs are intended to be sold as building blocks for use in design of a diagnostic test by the test developer. If an ASR is promoted as being intended for use with a particular instrument, FDA would not view the promoted product as an ASR. Use of the ASR with the particular instrument would be a design choice by the ASR manufacturer and not by the test developer. As a result, manufacturers should not promote specific laboratory instruments for use in conjunction with particular ASRs.

In contrast, open instruments that have user-defined capabilities, which allow the user to select an instrument and an ASR independently, and define, optimize, and validate the test performance characteristics and interpretation criteria, may be promoted for use generally in LDTs (e.g., spectrophotometers, HPLC). If instrumentation is used for an ASR-based test, the laboratory should be able to select the instrumentation and validate the performance of the LDT on that instrument.

17. Can the manufacturer of an ASR help with the validation and verification of performance specifications of a test that utilizes its ASR?

If a manufacturer or distributor wishes to market its product as an ASR, it should not assist with the development or validation of an LDT using its specific ASR. Under the CLIA regulations, the laboratory must conduct validation and verification of test performance specifications. 42 CFR 493.1213. This validation by the laboratory is the minimum requirement under CLIA for the laboratory to generate clinical results for tests of high complexity.

18. What type of information about a particular ASR can an ASR manufacturer provide to a laboratory?

An ASR manufacturer may provide laboratories with information, including peer-reviewed and published/presented literature, that establishes characteristics of the ASR itself, such as information describing the single ligand or target the ASR detects. Such information may not, however, describe the use of an ASR in a specific test, including information regarding an ASR's clinical utility and clinical performance as well as specific instructions-for-use and validation protocols. 21 CFR 809.30, 864.4020. When coupled with such information, the product would fall outside the definition of an ASR. See Section II, "What Meets the ASR Definition?".

IV. Research and Investigational Use of ASRs

19. Can ASRs be used for research?

Yes, ASRs can be used for research applications. The ASR requirements, including the need for the laboratory report disclaimer, apply only to clinical diagnostic use of these products and not to research applications. 21 CFR 864.4020(a)(2).

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

Products labeled for research use only (RUO) or investigational use only (IUO) are IVDs in different stages of development.

- FDA considers RUO products to be products that are in the laboratory research phase of development, that is, either basic research or the initial search for potential clinical utility, and not represented as an effective in vitro diagnostic product. 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 must be labeled “For Research Use Only. Not for use in diagnostic procedures.” as required under 21 CFR 809.10 (c)(2)(i).
- FDA considers IUO products to be products that are in the clinical investigation

phase of development. They may be exempt from the investigational device (IDE) requirements of 21 CFR Part 812 (21 CFR 812.2(c)), or may be regulated under 21 CFR Part 812 as either a non-significant risk device or a significant risk device. Diagnostic devices exempt from IDE requirements cannot be used for human clinical diagnosis unless the diagnosis is being confirmed by another, medically-established diagnostic product 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." 21 CFR 809.10(c)(2)(ii).

21. What is the difference in GMP requirements for manufacturers of an ASR versus an RUO reagent?

Manufacturers establish and follow cGMPs, as established in the quality system regulation, to help ensure that their products are manufactured under controlled conditions that assure the devices meet consistent specifications across lots and over time. ASRs must be manufactured following cGMPs. 21 CFR 809.20. FDA does not expect RUO reagents to be manufactured in compliance with cGMPs because products labeled as RUO reagents cannot be used as clinical diagnostic products. 21 CFR 809.10(c)(2)(i).