

# Draft Guidance for Industry and FDA Staff

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## Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions

### *DRAFT GUIDANCE*

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Food and Drug Administration  
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Office of In Vitro Diagnostic Device Evaluation and Safety

# **Preface**

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# Draft Guidance for Industry and FDA Staff Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions

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## INTRODUCTION

This draft guidance document is intended to clarify the regulations regarding commercially distributed analyte specific reagents (ASRs) (21 CFR 809.10(e), 809.30, and 864.4020),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. Below we have listed some frequently asked questions and FDA's Office of In Vitro Diagnostic Device Evaluation and Safety's (OIVD'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 As noted in this draft guidance document, ASRs are the building blocks of laboratory-developed tests. (See section II of this guidance.) ASRs are defined and classified in a rule codified at 21 CFR 864.4020. With this draft guidance document, FDA seeks to advise ASR manufacturers that it views the following practices as being inconsistent with the marketing of an ASR, as defined under 21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, laboratory equipment, 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 part of a test system.<sup>1</sup>

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**

This draft guidance document reflects our careful review of what we believe are the relevant issues related to ASRs and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

## **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 in vitro diagnostic devices that are regulated by FDA. They are subject to general controls, including the Quality System Regulation (QSR) (21 CFR Part 820), as well as the specific provisions of the ASR regulation (21 CFR 809.10(e), 809.30, 864.4020).

#### **2. What is the ASR rule?**

This guidance document refers to three rules as “the ASR rule.” The rules, published in 1997, include rules that 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)).

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<sup>1</sup> FDA's use of the term “test system” in this guidance document is not linked to definitions in 42 CFR Part 493. See question 8 for discussion of what FDA considers a “test system.”

### **3. What was the objective of the ASR rule?**

The ASR rule was designed to accomplish several policy objectives. These include ensuring the quality of materials used as components of in-house laboratory tests, and providing appropriate labeling so that healthcare users would understand how these tests were being validated. 62 FR 62244. FDA adopted the approach of regulating most ASRs using general controls and exempting them from premarket notification requirements as the least burdensome approach. This approach relies primarily on current Good Manufacturing Practices (cGMPs), medical device reporting, and labeling requirements, along with the Clinical Laboratory Improvement Amendments (CLIA), 42 U.S.C. 263a, to adequately control the risks associated with these devices. 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. 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 in-house tests that are developed using ASRs. 21 CFR 809.30(f). Another restriction requires the laboratory that develops an in-house test 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 to quickly and accurately detect [a mutation] associated with [a disease]."

In addition, the rule classifies certain ASRs as Class II or III devices that are subject to premarket notification or premarket approval application requirements in addition to the general controls described above.

### **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

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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).

## **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.

## **II. What Meets the ASR Definition?**

The ASR definition has given rise to confusion about which products fall within and outside of its bounds. Some of this confusion arises because a product that might in some circumstances be an ASR, will no longer be one due to its marketing and claims.

In the preamble to the ASR rule, FDA stated that ASRs may be thought of as 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 have been cleared or approved by FDA and also by clinical laboratories that use the ASRs to develop in-house tests used exclusively by that laboratory. 62 FR 62243, 62244. This is in contrast with 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. FDA designed the ASR rule to require that ASR manufacturers take certain actions, such as following cGMPs, to help ensure the safety and effectiveness of their devices. A premise underlying the rule, however, is that laboratories, rather than ASR manufacturers, develop the test in which the ASR is used and provide all necessary verification and validation.

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

- a single moiety;
- a single endpoint;
- no instructions or performance claims; and
- not promoted for use on specific instruments or in specific tests or test systems.

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

Examples of molecules that are ASRs are a single antibody (e.g., an anti-troponin I antibody), a single nucleotide primer (e.g., a forward primer for amplification of the  $\Delta F508$  locus of the gene encoding the cystic fibrosis transmembrane regulator (CFTR)), and a single purified protein or peptide (e.g., purified estrogen receptor protein or 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., cystic fibrosis genotyping, identification of cardiac risk).

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

- Multiple moieties (e.g., antibodies, probes, primers) bundled together in a pre-configured or optimized manner so that they are intended to identify and quantify more than one chemical substance or ligand. Such products are not ASRs because ASRs are defined as intended for use in "identification and quantification of an *individual* chemical substance or ligand in biological specimens." 21 CFR 864.4020(a) (emphasis added). As a result, FDA considers such products to be test systems, rather than ASRs. This means that products that might be ASRs when marketed individually, would not be considered ASRs when combined or multiplexed because they are no longer intended to identify an "individual chemical substance." ASRs are intended to be individual building blocks of tests that a laboratory develops. When a manufacturer combines ASRs, it has taken steps to build a particular test.
- Test systems. FDA considers a product a test system rather than an ASR when it includes more than a single ASR (i.e., it 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.
- Control material.
- Products that have specific performance claims, or procedural instructions, or interpretations for use.
- Reagents that are extensively processed (e.g., arrayed on beads). This type of modification is an optimization of the reagent to create a particular intended use that is more specific than the broad intended use described in the ASR definition. 21 CFR 864.4020(a).
- Reagents offered with software for interpretation of results.
- Products that do not meet the ASR definition, such as software for interpretation of assay results, or microarrays.

## **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 be able to be combined with, or used in conjunction with more than one ASR. In contrast, as stated above, an ASR is a specific chemical component, probe, or antibody that can detect an individual chemical substance or ligand. An ASR is considered the “active ingredient” or “building block” of a laboratory-developed test.

## **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 individual “building blocks” of laboratory tests and GPRs may not be intended for a specific diagnostic application. 21 CFR 864.4010, 864.4020. Although a GPR may consist of a single substance or a formulation of multiple substances as defined by 21 CFR 864.4010, it should be intended for general rather than specific use. 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 laboratory-developed tests. Therefore, a manufacturer who wishes to market its products as GPRs or ASRs should not promote or sell them together, including in test system configurations.

We recommend that manufacturers who wish to market products as ASRs, rather than as test systems, avoid listing ASRs, GPRs, and/or controls in catalogues, web sites, and other promotional materials, in small groupings that suggest these devices should be used together for

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a specific purpose. For example, primers specific for Factor V, Factor II, and MTHFR listed together with complementary probes and control material suggest that this group of reagents may be used together as a type of thrombophilia panel. Manufacturers who wish to promote products together in this manner should submit a PMA or 510(k) to FDA for approval or clearance of a test system.

To avoid promoting products as test systems rather than as separate ASRs and GPRs, we recommend that manufacturers list ASRs and GPRs in a fashion that is not associated with use in a particular test (e.g., alphabetically, or by reagent type [primers together, buffers together]).

**12. Can the manufacturer include instructions with an ASR?**

ASR manufacturers should not provide such instructions with an ASR. As explained above, FDA views reagents that are sold with instructions for developing or performing a test as test systems rather than as ASRs because an ASR is a building block for laboratory-developed tests and has no analytical or clinical performance claims. 21 CFR 809.10(e)(1)(x), 809.30(d)(4). Instructions for use of an ASR in a particular test 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 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, 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?**

Manufacturers and distributors should not make claims to physicians or laboratories regarding analytical or clinical performance for ASRs. The laboratories, not the manufacturers or distributors, should be responsible for the performance of the test. 21 CFR 809.30(d)(4). In addition, manufacturers should take care to avoid names for their ASRs that describe a specific clinical use.

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 what the ASR is specific for but does not claim to produce a particular clinical or analytical result. But a name such as "Cystic Fibrosis 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 with an ASR may make it appear that the manufacturer is actually marketing a test system, 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 a manufacturer chooses to market software for use with its product, then the products together would be considered a test system, rather than an ASR. ASR manufacturers should not promote or sell software for use with a particular ASR.

**16. What types of instrumentation can manufacturers promote for use with laboratory-developed tests?**

Manufacturers should not promote closed system laboratory instruments (i.e., when the user does not have the ability to modify instrument settings, or the design of the instrument allows only a specific proprietary reagent technology or assay method to be used) for use in conjunction with particular ASRs. FDA would consider promotion of such instrumentation with a specific ASR to be promotion of a test system.

In contrast, open system instruments that have user-defined capabilities, which allow the user to define, optimize, and validate the test performance characteristics and interpretation criteria, may be promoted for use generally in laboratory-developed tests. Examples of these instruments include spectrophotometers, HPLC, and flow cytometers. The instrumentation should be able to run various assays, allow parameter modification, or have a user interface that the laboratory can modify to define specific parameters for their laboratory-developed assay. If instrumentation is used, the laboratory should select the instrumentation and validate the performance of the laboratory-developed assay on that instrument.

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

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

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

A manufacturer may provide laboratories with information, including peer-reviewed and published/presented literature, limited to characteristics of the ASR itself. If a manufacturer intends to market its products as ASRs, it should not promote its products with literature and other materials that include information on use of the ASR in a specific test or test system. This would include information regarding an ASR's clinical utility and clinical performance as well as specific instructions-for-use and validation protocols. FDA views this type of information, when provided by the manufacturer, as evidence of intent to market a test system with instructions for use and validation. FDA would not view a product that is promoted with such information as an ASR.

**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).