

**Comparison of draft and final versions of the Food and Drug Administration’s guidance,
“Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions”**

	Draft ASR Guidance	Final ASR Guidance
Introduction	“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.”	Language added: “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.” “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. ”
Least Burdensome Approach	“This draft guidance document reflects our careful review of what we believe are the relevant issues related to ASRs and what we believe would be the least burdensome way of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.”	Language replaced with: “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 .”
FAQ # 1 What is the definition of an ASR?	“ASRs are in vitro diagnostic devices”	Language replaced with: “ASRs are medical devices”
FAQ #3 What was the		Language added:

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objective of the ASR rule?		“One of the primary goals of the rule was to ensure the quality of the primary, active reagents of finished IVDs or LDTs.”
FAQ # 4 What does the ASR rule require?	“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.”	(language removed)
FAQ # 5 Are some ASRs Class II or Class III, requiring a premarket submission?		Language added: “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.”
FAQ # 6 How does a manufacturer know whether its device is an ASR?	“Manufacturers who wish to obtain FDA advice on this matter in advance of marketing may consult with OIVD.”	Language added: “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. ”
What Meets the ASR Definition	“Based upon this description, together with the ASR definition, FDA views an ASR as having the following characteristics: <ul style="list-style-type: none"> • a single moiety; • a single endpoint • no instructions or performance claims; and • not promoted for use on specific designated instruments or in specific tests or test systems.” 	Language replaced with: “Based upon this description, together with the ASR definition, FDA views an ASR as having the following characteristics: <ul style="list-style-type: none"> • 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.”
FAQ # 7 What are some examples of entities that FDA considers to	“Based upon this description, together with the ASR definition, FDA views an ASR as having the following characteristics: <ul style="list-style-type: none"> • used to detect a single ligand or target (e.g., 	Language replaced with: “Examples of entities that are ASRs include: <ul style="list-style-type: none"> • a single antibody (e.g., an anti-troponin I polyclonal or monoclonal antibody,

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<p>be ASRs?</p>	<p>protein, single nucleotide change, epitope);</p> <ul style="list-style-type: none"> • not labeled with instructions for use or performance claims; and • not promoted for use on specific designated instruments or in specific tests.” 	<p>whether untagged or tagged, e.g., conjugated to horseradish peroxidase),</p> <ul style="list-style-type: none"> • a single forward/reverse oligonucleotide primer¹ pair (e.g., a primer pair for amplification of a single amplicon, such as for amplification of the $\Delta F508$ locus of the gene encoding the cystic fibrosis transmembrane regulator (CFTR)), or single forward or reverse primer individually, • a nucleic acid probe² (whether untagged or tagged, e.g., conjugated to biotin or CyTM3) 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). <p>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).</p> <p>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”</p>
<p>FAQ # 8 What are some examples of entities that FDA does not consider to be ASRs?</p>	<p>“• Multiples 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 ASR are defined as intended for use in “identification and quantification or an individual chemical substance or ligand in biological specimens “ 21 CFR 864.4020(a) As a result, FDA considers such products to be test systems, rather than ASRs. This means that products</p>	<p>Language replaced with:</p> <p>“• 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.</p> <ul style="list-style-type: none"> • 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

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	<p>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 test that a laboratory develops. When a manufacturer combines ASRs, it has taken steps to build a particular test</p> <ul style="list-style-type: none"> • 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 as instructions for use • Control material • Products that have specific performance claims, or procedural instructions, or interpretations for use • Reagents that 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” 	<p>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.</p> <ul style="list-style-type: none"> • 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. <p>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 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.</p> <p>Other types of devices that do not meet the definition of an ASR include:</p> <ul style="list-style-type: none"> • 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. <p>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.”</p>
FAQ # 9	“An ASR is considered the “active ingredient” or “building block” of a laboratory-developed test.”	(language removed)

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<p>How do General Purpose Reagents compare to ASRs?</p>		
<p>FAQ # 11 Can a manufacturer or distributor promote specific ASRs and GPRs for use together in developing a test?</p>	<p>“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, websites and other promotional materials, in small groupings that suggest these devices should be used together for 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.</p> <p>To avoid promoting products as test systems rather than as ASRS or 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].”</p>	<p>Language replaced with:</p> <p>“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.”</p>
<p>FAQ # 12 Can the manufacturer include instructions with an ASR?</p>	<p>“ASR manufacturers should not provide instructions with an ASR.”</p>	<p>Language added:</p> <p>“ASR manufacturers should not provide instructions for developing or performing an assay with an ASR”</p>
<p>FAQ # 13</p>	<p>“But a name such as ‘Cystic Fibrosis ASR’</p>	<p>Language replaced with:</p>

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<p>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?</p>	<p>describes a specific clinical use for the product and FDA, therefore, would consider such a product to be an ASR.”</p>	<p>“But a name such as ‘Cardiac Risk ASR’ describes a specific clinical use for the product and FDA, therefore, would consider such a product to be an ASR.”</p>
<p>FAQ # 15 Can a manufacturer or distributor market software for use with an ASR?</p>		<p>Language added: “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.”</p>
<p>FAQ # 16 What types of instrumentation can manufacturers promote for use with LDTs?</p>	<p>“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”</p>	<p>Language replaced with: “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.”</p>