

# Pathway to commercialization for an *in vitro* diagnostic (IVD) in the US

The US Food and Drug Administration (FDA) defines *in vitro* diagnostics as “those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.”<sup>1</sup>

For manufacturers of *in vitro* diagnostic tests, there are three potential avenues to access the US market—with an analyte specific reagent (ASR), a laboratory-developed test (LDT) or an *in vitro* diagnostic (IVD). This article defines each of these types of tests and summarizes the pertinent regulations of each category.

Exhibit 1 summarizes the regulatory body that regulates each type of test, how the test is regulated, and who can buy the test.

## Exhibit 1: Summary of types of diagnostic tests and how they are regulated

Type of test	Who regulates it	How is it regulated	What is sold	Who can buy it
ASR	FDA	Medical device regulations	Reagent	Other IVD manufacturers, CLIA labs, non-clinical labs
LDT	CMS	CLIA laboratories	Service	Clinics, patients, third-party payers
IVD	FDA	Medical device regulations	Diagnostic	General market, POC, clinics, etc.

ASR: Analyte specific reagent

LDT: Laboratory-developed test

IVD: *In vitro* diagnostic

FDA: Food and Drug Administration

CMS: Centers for Medicare and Medicaid Services

CLIA: Clinical Laboratory Improvement Amendments

POC: Point of care

Source: [www.fda.gov](http://www.fda.gov)

## Analyte specific reagents

Analyte specific reagents (ASRs) are defined by the FDA 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.”<sup>2</sup>

<sup>1</sup> US Department of Health & Human Services, Food and Drug Administration. (2009, April 1.) CFR - Code of Federal Regulations Title 21. CFR 809.3. Retrieved March 9, 2010, from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=809.3>

<sup>2</sup> US Department of Health & Human Services, Food and Drug Administration. (2009, April 1.) CFR - Code of Federal Regulations Title 21. CFR 864.4020(a). Retrieved March 9, 2010, from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=864.4020>

ASRs are typically classified as [class I devices](#) and are subject to general controls and current Good Manufacturing Practices (GMP). As well, they must comply with “the ASR rule,” which imposes restrictions on the sale, distribution and use of ASRs and establishes labelling requirements (For more details, visit <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071269.pdf>.) The FDA exempts manufacturers who sell ASRs from pre-market notification requirements.

Manufacturers are prohibited from making any advertising or promotional claims for clinical and analytical performance of ASRs. ASRs must be labelled as follows: “Analyte Specific Reagent. Analytical and performance characteristics are not established.”

Note that some ASRs are considered [class II or class III devices](#), and these are regulated according to their classification.

ASRs are often active ingredients of tests that are used to identify a disease or condition. The ASRs are purchased by manufacturers who then use them as components in tests that are cleared by the FDA, or in LDTs (laboratory-developed tests) which are sold under Clinical Laboratory Improvement Amendments (CLIA) regulations (see below). Laboratories that develop tests that contain ASRs must comply with CLIA.

According to the FDA, an ASR must have the following three characteristics:

- it is used to detect a single ligand or target
- it is not labelled with instructions for use or performance claims
- it is not promoted for use on specific designated instruments or in specific tests<sup>3</sup>

Manufacturers are only permitted to sell ASRs to manufacturers of *in vitro* diagnostics, CLIA labs, 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 non-clinical laboratories).

It should be noted that ASRs are distinct from “research-use only” (RUO) products. Diagnostics designated as RUO are at a different stage of development. For example, they could be diagnostics at the clinical stage of testing. Also, ASRs are required to be manufactured according to cGMP (current Good Manufacturing Practices) whereas RUO reagents may not necessarily meet this requirement as they are not used as clinical diagnostic products.

### Laboratory-developed tests

Laboratory-developed tests (LDTs) are tests developed by a single clinical laboratory for use only in that laboratory. Companies that opt to offer LDTs are able to access the market relatively quickly as formal FDA approval is not required for commercialization.

Companies offering to sell an LDT must first ensure the lab is certified according to CLIA (see below). The limitation of an LDT is that it cannot be used to specify a diagnosis. A manufacturer is only permitted to state the correlation of the outcome of the test with a likely outcome. The test results must be labelled as follows: “This test was developed and its performance characteristics determined by [laboratory name]. It has not been cleared or approved by the Food and Drug Administration.” (US Code of Federal Regulations Title 21 Chapter 1, Subpart H, 809.30, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=809.30>).

The requirements for CLIA certification are based on the complexity of the test and not the type of laboratory where the testing is performed.

In the US molecular diagnostic cancer testing marketing, it is estimated that 98% of revenues are derived from CLIA labs rather than FDA-approved products.<sup>4</sup>

### Clinical Laboratory Improvement Amendments (CLIA)

CLIA was passed by the US Congress in 1988 to establish quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed. The Centers for Medicare & Medicaid Services (CMS) regulates all laboratory testing (except research) performed on humans in the US through CLIA. However, the categorization of commercially marketed IVDs under CLIA remains the responsibility of the FDA. There are three types of regulatory categories under CLIA, based on the potential risk to

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<sup>3</sup> US Department of Health & Human Services, Food and Drug Administration, Center for Devices and Radiological Health. (2007, September 14). *Guidance for Industry and FDA Staff—Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions*. Retrieved March 9, 2010, from <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071269.pdf>

<sup>4</sup> MaRS Discovery District. (2009, September). *Life Sciences: Molecular Diagnostics—New Tools for Evidence-Based Medicine*. Retrieved March 9, 2010, from <http://www.marsdd.com/buzz/reports/moleculardiagnosics>

public health:

- waived tests
- tests of moderate complexity
- tests of high complexity

### Waived tests

Tests can be waived from regulatory oversight if they meet certain requirements. Such tests include simple laboratory examinations and procedures cleared by the FDA for home use, tests that employ methodologies so simple and accurate they render negligible the likelihood of erroneous results, and tests that pose no reasonable risk of harm to the patient if performed incorrectly.<sup>5</sup> Examples of waived tests are pH dipstick tests, urine pregnancy tests, home blood glucose monitoring kits, and ovulation kits.

Waivers can also be granted for tests if the manufacturer can demonstrate they meet the statutory criteria and it can provide valid scientific data to verify the waiver criteria have been met.

### Moderate and high-complexity tests

Non-waived tests are categorized according to complexity. There are seven criteria, and a test is assigned a complexity score of 1, 2 or 3 on each criterion (with 1 being low in complexity). Tests with total scores of 12 or less are considered to be of moderate complexity, while tests with scores higher than 12 are high in complexity. The seven criteria are:

- knowledge required to perform the test
- training and experience required to perform the test
- reagents and materials preparation
- characteristics of operational steps
- calibration, quality control, and proficiency testing materials
- test system troubleshooting and equipment maintenance
- interpretation and judgement<sup>6</sup>

Laboratories that perform tests of moderate complexity are required to satisfy certain criteria related to experienced personnel and quality management, and must undergo a biannual inspection. Moderate-complexity tests include urine culture and colony count kits, gram stain tests, tests to detect occult blood in body fluids, and tests to isolate and identify aerobic bacteria from throat, urine, cervical or urethral specimens.

Laboratories that perform tests of high complexity are required to satisfy more stringent criteria related to experienced personnel and quality management. These labs are also required to undergo a biannual inspection. Examples of high-complexity tests include serogrouping and typing tests, antigen or toxin test procedures or kits requiring microscopic evaluation, radioimmunoassays, and gel-based immunochemical procedures.

For a full list of all the tests the FDA considers to be of moderate or high complexity, visit <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm>.

### *In vitro* diagnostic multivariate index assays

Laboratory-developed *in vitro* diagnostic multivariate index assays (IVDMIA) are a subset of LDTs. According to the FDA, IVDMIA raise significant issues of safety and effectiveness. These types of tests are developed based on correlations between multivariate data and clinical outcome. The clinical validity of the test claims is not usually immediately transparent to patients, laboratory technicians and clinicians. In 2007, the FDA issued a draft guidance document seeking to regulate IVDMIA as a discrete category of device that should meet pre-market and post-market regulatory requirements.

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<sup>5</sup> US Department of Health & Human Services, Food and Drug Administration. (2009, June 19). *CLIA Waivers*. Retrieved March 9, 2010, from <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRRegulatoryAssistance/ucm124202.htm>

<sup>6</sup> US Department of Health & Human Services, Centers for Disease Control and Prevention. (2004, July 7.) *CLIA: Subpart A—General Provisions*. Retrieved April 22, 2010, from [http://wwwn.cdc.gov/clia/regs/subpart\\_a.aspx#493.17](http://wwwn.cdc.gov/clia/regs/subpart_a.aspx#493.17).

The FDA defines an IVD MIA as a device that meets both these criteria:

- combines the value of multiple variables using an interpretation function to yield a single, patient-specific result that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease
- provides a result whose derivation is non-transparent and cannot be independently derived or verified by the user<sup>7</sup>

Examples of IVDMIAs include gene-expression profiling for breast-cancer prognosis, or a device that integrates quantitative results from multiple immunoassays to obtain a qualitative score that predicts a person's risk of developing a certain disease or condition.

The FDA proposes to regulate IVDMIAs in the same way as other medical devices (i.e., class II or class III devices) with all the associated requirements.

### **In vitro diagnostic tests**

*In vitro* diagnostic tests (IVDs) are the most highly regulated diagnostics. IVDs are considered medical devices, and thus are regulated by the FDA's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), at the Centers for Device and Radiological Health (CDRH). IVDs are subject to pre-market and post-market controls as well as CLIA.

Manufacturers seeking FDA approval of an *in vitro* diagnostic test are required to determine the category of the test/device, compile the necessary information to support the proposed claims for its use, and obtain FDA clearance to market the test. All tests cleared under the medical-device regulations must be labelled "For *in vitro* diagnostic use." In addition, all manufacturers must comply with current Good Manufacturing Practices.

For detailed information on medical devices, their classifications and the requirements they must meet for approval, see the article, [How medical devices are approved in the US](#). A brief summary is provided below.

### **Medical device categorization**

Medical devices are categorized as class I, II or III. The regulatory requirements increase in stringency from class I to class III. The class of device determines the submission requirements to apply for approval for commercialization. The classification of a device depends on the intended use of the device, its indications for use, and, importantly, the level of risk the device poses to the patient or user.

**Class I:** This group covers devices subject to general controls. Most class I devices are *exempt devices*.<sup>\*</sup> Some require a 510(k) submission (see [How medical devices are approved in the US](#)).

**Class II:** This group covers devices subject to general and special controls. Most class II devices are approved under a 510(k) pre-market notification submission, but some are exempt devices.

**Class III:** This group covers devices subject to general controls, special controls and pre-market clearance. Most class III devices are approved under a pre-market approval (PMA) procedure.

<sup>\*</sup>*Exempt devices* are those specifically exempted by regulation, and pre-amendment devices. A pre-amendment device is one that was marketed prior to 1976 and has not been modified, and the FDA has not published a regulation requiring a pre-market approval procedure.

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## **Exhibit 2: Summary of device classifications and target approval times in the US**

	<b>Class I</b>	<b>Class II*</b>	<b>Class III</b>
Type of application	Exempt	510(k)	PMA
Target review time	Registration	90 days	180 days

\* Some class II devices are deemed exempt.

Source: [www.fda.gov](http://www.fda.gov)

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<sup>7</sup> US Department of Health & Human Services, Food and Drug Administration. (2007, July 26). *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff—In Vitro Diagnostic Multivariate Index Assays*. Retrieved March 10, 2010, from <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.pdf>