

Industry Whitepaper

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*Types of in vitro Diagnostics:
Clearing up the Confusion*

Types of *in vitro* Diagnostics

All IVDs for human use are medical devices, that much is clear. Soon after that, though, it is easy to get lost in a seemingly foreign language of acronyms – ASRs, RUOs, LDTs, and more. Can you explain the differences between ASRs and LDTs – not to mention RUOs, IUOs, homebrew tests, and companion IVD diagnostics? How do you even begin to know what category your new device will fall into?

The FDA has several good guidance documents on these subjects, all of which are readily available on the internet, but reading any one takes at least an hour; digesting it takes even longer. And then you may just discover that the document you read doesn't even apply to your device. If someone would just tell you what your device would be considered as, you could focus your time on the correct documents, instead of chasing down rabbit holes.

We will start with the basics. A medical device is officially defined as:

“an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--

- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
 - (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
 - (3) intended to affect the structure or any function of the body of man or other animals, and
- which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.”¹

Under that same section of the law, all IVDs for human use are medical devices. They are further defined officially as “those reagents, instruments, and systems intended for use in the 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.”² The key words here are “*in vitro*”, meaning that the item is not for use in the body- these are literally, tests that are run outside the body on samples of tissue or blood, etc.

Under the IVD umbrella, there are many different categories, and here is where the waters get murky. This paper will consider the following types of IVDs:

- RUOs (Research Use Only),
- IUOs (Investigational Use Only)
- ASRs (Analyte Specific Reagents)
- LDTs (Lab Developed Tests)
- Companion Diagnostic IVDs
- IVDMIAs (*in vitro* diagnostic multivariate index assay)

For the sake of discussion, we will also add to the list above, GPRs (General Purpose Reagents). Although they are not IVDs, GPRs are frequently used in conjunction with IVDs, so it is important to understand their usage limitations as well.

RUOs

The regulatory path of a diagnostic typically starts as an RUO, and progresses to an IUO. After the IUO stage, the path forks into multiple directions.

¹ 21 U.S. Code § 321 (h)

² 21 CFR 809.3

Even though an RUO diagnostic is a very early step on the regulatory path, it is still considered to be an IVD. RUO products are just that – research products. They are in the early stages of development and are used for basic laboratory research and/or the early search for potential clinical utility.

RUOs are not labeled for a specific clinical use, and they cannot be used for a diagnosis. RUO products must be labeled “For Research Use Only. Not for use in diagnostic procedures.”

Since they cannot be used clinically, RUO products are exempt from the Medical Device Reporting (MDR) requirements (the reporting of adverse events). They are also exempt from compliance with the Quality System Regulations (QSReg, formerly “GMPs”), from registration/listing requirements and from pre-market notification requirements (submission of a 510(k) or PMA). While not having to do a premarket notification for an RUO device, is nice, it also means that you cannot make claims about your device - which means that you won’t make much money.

However, just slapping an RUO or IUO label on an IVD product does not make the device exempt from these otherwise applicable regulations. You have to walk the walk, as well. In fact, the FDA may well decide that the device is actually intended for use in clinical diagnosis based on how you present it, including how the device is marketed. Therefore, it is important to monitor how your products are presented to the marketplace in terms of advertisements, marketing claims, technical support, etc.

RUOs and IUOs are covered in more detail within a single guidance document from the FDA³.

IUOs

IUOs are a bit farther along on the regulatory path. These are products that are “being shipped or delivered for product testing that is not subject to 21CFR part 812... ...prior to full commercial marketing”. Typical IUO use scenarios for IVDs would be, for instance, comparison studies to determine performance characteristics.⁴

A key point is that IUO devices are not the same thing as an IDE device, which is undergoing testing for safety and effectiveness, and is therefore subject to the IDE regulations. This frequently causes confusion. IUO status applies only to those devices that are exempt from the IDE regulations.

Like RUOs, IUOs are also considered to be IVDs. Also like RUOs, IUOs cannot be labeled for a specific clinical or diagnostic use. IUOs can be used to contribute to a clinical diagnosis, but confirmation by the use of another medically accepted test or procedure is always required.

The labeling of an IUO device is required to have a disclaimer, similar to that of an RUO. In the case of IUO devices, the disclaimer must state “For Investigational Use Only. The performance characteristics of this product have not been established”. (This is as opposed to the labeling of devices that are subject to the IDE regulations, which must state “CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use.”.)

Also similar to RUOs, an IUO device is exempt from the MDR Reporting requirements, as well as the requirements for QSReg compliance, registration/listing, and pre-market notification requirements (submission of a 510(k) or PMA)

³ <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm>

⁴ <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm>

ASRs

The official definition of an ASR can be found in the reference table included in this white paper⁵. However, to paraphrase quite a bit, an ASR is a compound used to detect a single target or ligand. ASRs can be considered the active ingredient in a given test. They often serve as the building blocks of a lab-developed test.

ASRs, as a class, are subject to MDR Reporting, establishment registration, and device listing. They are also subject to the QS Regs (a.k.a. “GMPs”).

Within the FDA guidance document regarding ASRs⁶, the FDA clearly calls out what they consider to meet the criteria of being an ASR, as well as what does not. Just some of the examples that the FDA considers to NOT be ASRs include: microarrays, products containing multiple ASRs packaged together, and products with specific performance claims.

Most ASRs are Class 1 devices, and therefore are exempt from premarket notification requirements. Class I ASRs, like other Class I devices, are subject to general controls (a term used to signify an abbreviated version of the QSReg).

ASRs used for bloodbanking tests, however, are usually considered to be Class II, while ASRs used for diagnosis of contagious or high risk diseases tend to be Class III. ASRs that are Class II or Class III are subject to premarket notification requirements as well as the full version of the QSReg.

All ASRs can be used for clinical diagnostic tests. However, in the case of a Class I ASR, the ASR may only be used clinically as part of a lab-developed test. Federal law prohibits manufacturers from making any analytical or clinical claims in regard to Class I ASRs. In fact, the labeling of the Class I ASR itself, and any results reported must contain the disclaimer “Analyte Specific Reagent. Analytical and performance characteristics are not established.” Manufacturers must be careful to ensure that their promotional materials do not overstep this boundary. If one wishes to make analytical or performance claims, they must submit a premarket notification and have the class changed to Class II or Class III.

LDTs

Lab-developed tests are those tests that were once referred to as “home brews” or “in-house” tests. These are tests that a laboratory develops on their own, often using ASRs as the active ingredient.

The regulatory framework for LDTs is changing, and not in a small way. On July 31, 2014, The FDA has submitted to Congress, a draft guidance outlining their intentions regarding how they will regulate LDTs in the future.⁷

Labs that develop and use LDTs have been subject to CLIA (Clinical Laboratory Improvement Amendments) regulations since 1988. The CLIA requirements are enforced under the Centers for Medicare and Medicaid Services (the CMS), not under the FDA.

This is an important difference. The CLIA program regulates laboratories that perform testing on patient specimens in order to ensure accurate and reliable test results. The FDA regulates manufacturers and devices to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective. These are two very different areas of focus. As noted in the draft guidance, CLIA regulations focus on the quality of the laboratory processes for using devices, rather than on the design and manufacture of the devices themselves.

⁵ 21 CFR 864.4020(a)

⁶ <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm078423.htm>

⁷ <http://www.fda.gov/downloads/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm407409.pdf>

In the past, the FDA has chosen to “practice enforcement discretion” in regard to LDTs. Loosely translated, this means that the agency did not see them as a major risk and chose to deploy their limited resources elsewhere. But times change.

As lab-developed tests become more complex, and the internet shrinks distances, LDTs that were once manufactured in small volumes by a local laboratory may now be used widely to screen for diseases or to direct critical treatment decisions. To further complicate matters, since a disclaimer is not always required when reporting results from these tests, physicians may not be aware that the test results they are reviewing are from an LDT. Additionally, LDTs may be directly marketed to consumers, who are almost never aware of these nuances.

CLIA regulations do not ensure the safety and effectiveness of a device. They don’t require reporting of adverse events, and they don’t require the removal of unsafe devices from the market. Nor do they assess the quality of the manufacturing of the devices.

For all of these reasons (and more), the FDA is choosing to no longer practice enforcement discretion toward all LDTs. Exceptions are made for LDTs used solely for forensics (law enforcement) purposes and certain LDTs for transplantation, along with a few other types – the FDA will continue to practice enforcement discretion towards these LDTs.

All LDTs will become subject to registration/listing requirements, as well as reporting of adverse events. However, only Class II and Class III LDTs will be subject to premarket review requirements and quality system requirements.

Six months after the finalization of the draft guidance, all manufacturers of LDTs (regardless of Class) must notify the FDA if they are developing and/or manufacturing LDTs (“the notification process”) and must begin to report significant adverse events to the agency.

Within 18 months of the finalization date of the guidance, the FDA intends to publish a guidance on what they consider to be Class I, II, or III.

The FDA plans to prioritize LDTs using a risk-based approach, and phase-in the premarket review requirements over an extended period of time. The prioritization of the highest risk LDTs (Class III) will be complete within 24 months of the date when the final guidance is published. The phase-in of premarket requirements (submission of a 510(k) or PMA) for Class III LDTs will begin 12 months after the final publication date, and will continue for five years.

Remember, however, that “high-risk” is not necessarily defined by the test population or even the disease state. A novel analyte in and of itself may cause a test to be considered high risk.

The prioritization of the moderate risk LDTs (Class II) will be complete within four years of the date when the draft guidance becomes final. The phase-in of premarket requirements for Class II LDTs will be complete within nine years.

There will be no premarket requirements for Class I LDTs, which are considered low-risk. However, exactly what will be considered as a Class I LDT remains uncertain until the publication of the promised draft guidance regarding classification, which, as mentioned above, is expected to be published within 18 months of the finalization of the draft LDT guidance.

The FDA plans to continue to practice enforcement discretion with respect to QSReg requirements until a manufacturer submits a PMA or the FDA issues a 510(k) clearance for the LDT. They also plan to practice enforcement discretion regarding registration and listing until the date specified by the priority list, if the lab participated in the notification process.

Laboratories that do not notify the FDA and provide basic information on their LDTs within six months of the finalization of the draft LDT guidance “will have opted not to be within the scope of FDA’s enforcement discretion policy with respect to the registration and listing requirements”. Again, loosely translated, this means that the lab just gave up the right to the delayed timeline, and immediately falls with the FDA’s normal enforcement approach.

If you manufacture an LDT, or if you even think your device might be an LDT, you really must read the draft guidance. It is very content-rich, and includes direction regarding what the FDA considers to NOT be LDTs. It also speaks to what the FDA plans to consider as high-risk LDTs (future Class III devices). For instance, screening devices for serious diseases intended for use in asymptomatic patients with no other confirmatory testing is performed (e.g. for malignant cancers), diagnostic devices for certain infectious diseases with high-risk intended users, and devices that act like companion diagnostics (discussed below).

IVDMIA

Another term you may hear tossed around is IVDMIA (*in vitro* diagnostic multivariate index assay)⁸. The FDA issued a draft IVDMIA guidance document in 2007, in which it defines an IVDMIA as a device that:

- (1) “Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a “classification,” “score,” “index,” etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and
- (2) Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.”⁹

In layman’s terms, these are typically multiplex tests that employ mathematical algorithms to “calculate” a person’s risk for a disease or response to a drug, based on their molecular profile.

The FDA has never finalized that draft guidance, and in fact, has publicly stated that they have decided not to do so for the foreseeable future. Since the agency considers IVDMIA as a subset of LDTs (and a high-risk subset at that), the agency feels that the LDT guidance will cover this arena adequately.

Companion IVD Diagnostics

An IVD companion diagnostic is an IVD that “provides information that is essential to the safe and effective use of a corresponding therapeutic product”.

On August 6, 2014, the FDA issued a final guidance document on IVD companion diagnostic devices.¹⁰ Within this guidance document, the FDA clearly states that IVDs that are not essential for the safe and effective use of a therapeutic product are not considered to be companion diagnostics.

The FDA also makes clear that, for devices that are companion diagnostics, the use of that companion diagnostic must be stipulated in the labeling of the therapeutic product, given that the companion diagnostic is essential for safe and effective use of the therapeutic product.

Likewise, the labeling of the companion diagnostic must specify the therapeutic product for which it has been approved or cleared for use. The agency does, however, recommend that the labeling of the therapeutic product refer to the use of an approved or cleared companion diagnostics, rather than a particular manufacturer’s companion diagnostic. This is being done in the hopes that this will facilitate the development of more than one companion diagnostic for the therapeutic product.

For novel therapeutic products, the FDA intends to review premarket applications for companion diagnostics at the same time as the application for the therapeutic product. They state within the guidance that they will not generally

⁸ <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071455.pdf>

⁹ <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm>

¹⁰ <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>

approve the new therapeutic or new indications for an existing therapeutic product if the companion diagnostic is not approved or cleared for that indication. The guidance does, however, allow for some exceptions to that rule, and examples of those scenarios are covered within the document.

The guidance speaks to other types of scenarios as well. For instance, if a manufacturer already markets an IVD, and now intends to market that IVD as a companion diagnostic for a new therapeutic product, the FDA will likely consider this as a new use for the IVD, and would require a new premarket submission.

New companion diagnostics and therapeutic products can be combined into one investigational study, but the study must meet the requirements for both the device IDE (investigational device exemption) regulations (21CFR812) as well as the IND (investigational new drug) regulations (21CFR312).

Manufacturers who are developing companion diagnostics would be well-advised to seek a meeting with the relevant device and therapeutic product review divisions at the FDA should they have any questions, in order to ensure a smooth review process down the road.

GPRs

A General Purpose Reagent (GPR) is defined as “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.”¹¹.

GPRs cannot be labeled for a specific clinical or diagnostic use. However, GPRs can be combined with and/or used in conjunction with ASRs by the laboratory or IVD manufacturer that develops the finished test.

GPRs are not IVDs, but are classified as Class I medical devices. Therefore they are subject to the requirements for registration/listing, and MDR reporting. Due to their status as a Class I medical device, GPRs are exempt from the requirements for premarket notification. Additionally, they are only subject to compliance with sections 820.180 (records) and 820.198 (complaint files) of the QS Regs, unless the GPR is sold as sterile.

One last word of caution

Although this paper focuses on medical devices, It is important to note that IVDs may also be considered to be biological products subject to section 351 of the Public Health Service Act ([42 U.S.C. 262](#)). This will apply mostly to e.g. diagnostic allergenic extracts, blood banking tests, and HIV testing. Be sure to check the regulations to make sure that they don't apply to your product.

Article authored by: Heidi Hancock Strunk, Regulatory Consultant, Pearl Pathways

¹¹ 21 CFR 864.4010(a)

	RUO	IUO	ASR	LDT	Companion IVD	GPR
Definition	"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"	"products that are in the clinical investigation phase of development... 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)."	"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."	"An IVD that is intended for clinical use and designed, manufactured and used within a single laboratory." Note that IVDMAs fall into this category.	"an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product"	"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."
In layman's terms	"basic research" and "is there potential clinical utility?"	"under investigation <u>and</u> exempt from IDE regs"	"the active ingredient"	"home brew" or "in-house" tests	"the test that goes with the drug or device"	"general lab reagent"
IVD?	Y	Y	Y	Y	Y	N
Specific Regulation	N/A	N/A	864.4020(a)	N/A	N/A	864.4010(a)
Labeled for a specific clinical or diagnostic use	N	N	N (Class I) Y (Class II or III)	Y	Y	N
Can be used for clinical diagnosis	N	Y (only with confirmatory test)	Y (Class I - only if part of an LDT) Y (Class II or III)	Y	Y	N (but may be utilized as part of an LDT)
Subject to QSRegs 21CFR820	N	N	Y	N (currently) Y (future)	Y	Y, but only records and complaints, unless sold as sterile
Registration and Listing required	N	N	Y	N (currently) Y (future)	Y	Y
Adverse event reporting required	N	N	Y	N (currently) Y (future)	Y	Y
Premarket notification requirements	N	N	Y	N (currently) Y (future)	Y	N

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