REGULATORY PATH FOR IN VITRO DIAGNOSTICS

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Introduction:

An in-vitro diagnostic (IVD) device usually comprises pathology tests and related instrumentation used to conduct testing on human bodily fluids or tissue samples to assist in clinical diagnosis.

Regulatory and legal requirements applied to IVDs are set within the changing landscape. In the US, IVDs are defined under 21 CFR 809 and are regulated under guidelines similar to medical devices. In the EU, IVDs are defined and regulated separately from other medical devices under a separate IVD Directive 98/79/EC. IVDs must comply with the essential requirements of Annex 1 of the directive and products must be CE marked to be legally marketed in EU.

Classification:

Classification dictates the pre-market process and amount of regulatory oversight. The data required for substantial claims has significant effects on the product development and marketing cost. The classification of IVDs varies in both the EU and the US. In the US, IVDs are classified as other medical devices with the regulatory control deemed necessary. Class 1 devices are under general control to provide reasonable assurance of their safety and effectiveness. Most Class I devices are exempt from premarket notification. Class 2 is under both general and special control. General controls alone are insufficient to provide reasonable assurance of their safety and effectiveness and for which establishment of special controls can provide such assurances. Special controls may include special labeling, mandatory performance standards, risk mitigation measures identified in guidance, and post market surveillance. Class 3 devices require general and special control with mandatory PMA approval.¹

Table 1: FDA IVD classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Level of risk</th>
<th>Controls</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>low to moderate</td>
<td>general controls</td>
<td>• Complement reagent, phosphorus (inorganic) test systems</td>
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<td></td>
<td>• E. coli serological reagent</td>
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<tr>
<td>Class 2</td>
<td>moderate to high</td>
<td>general controls and special</td>
<td>• Immunological test system</td>
</tr>
<tr>
<td></td>
<td>risk</td>
<td>controls</td>
<td>• Glucose test system</td>
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<td></td>
<td></td>
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<td>• Coagulation Instruments</td>
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<tr>
<td>Class 3</td>
<td>high risk</td>
<td>general controls and PMA</td>
<td>• Automated PAP smear readers</td>
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<td></td>
<td></td>
<td>(premarket approval)</td>
<td>• Nucleic Acid Amplification devices for Tuberculosis</td>
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<td>• Total prostate specific antigen (PSA) for the detection of cancer</td>
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In the EU, IVD devices are classified into four categories based on the risk and regulatory control. These classifications are General, Self-test, Annex II List A and Annex II List B.

Table 2: EU IVD classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Level of risk</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>General</td>
<td>Low Individual and Public Risk</td>
<td>• Specimen receptacle, a microbiological culture medium, enzyme immunoassay analyser</td>
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<td></td>
<td></td>
<td>• Tests for Hormones, Cardiac Markers, Hematology and Clinical Chemistry Tests</td>
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<tr>
<td>Self-testing</td>
<td>Risk increased due to use by lay users</td>
<td>• Pregnancy self-test, Urine strip test, Hormone home test</td>
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<tr>
<td>Annex II List A</td>
<td>High Individual and Public Risk</td>
<td>• Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell</td>
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<tr>
<td></td>
<td></td>
<td>• Reagents for determination for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D,</td>
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<tr>
<td>Annex II List B</td>
<td>Moderate risk</td>
<td>• Tests for irregular anti-erythrocytic antibodies.</td>
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<td>• Tests for rubella and toxoplasmosis</td>
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<td>• Tests for phenylketonuria</td>
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<td></td>
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<td>• Tests for cytomegalovirus and chlamydia</td>
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<td>• Tests for prostate-specific antigen</td>
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<td>• Tests and software for evaluating risk of Trisomy 21</td>
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<td></td>
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<td>• Self-tests for blood sugar</td>
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</table>

Regulatory Pathway

Diverse paths for obtaining US FDA approval:

For the Class I devices that are the subject of the guidance document, FDA intends to propose an amendment to the classification regulations to exempt these devices from 510(k) requirements that currently apply. While FDA proposes and finalizes these down classifications and exemptions, it will exercise enforcement discretion with regard to 510(k) submission requirements for the relevant devices.²
The devices subject to enforcement discretion includes the following:

- Clinical chemistry devices, such as iron (non-heme) test systems, breath-alcohol test systems, and others;
- Hematology devices, such as platelet-adhesion tests, euglobulin lysis time tests, and others;
- Immunology and microbiology devices, which include hemoglobin immunological test systems.

For US Market approval, there are several factors other than classification that influence the process for regulatory approvals (Figure 1).

- If the new test can be shown to be substantially equivalent to an existing device which is considered as predicate device, then the 510(k) is the regulatory path for approval.
- If new diagnostic technology cannot be considered substantially equivalent to an existing technology, and will be used to make a critical medical decision concerning the diagnosis, treatment, or medical management, then the premarket approval (PMA) is the regulatory path of choice.
- If no predicate device exists and the test is of low or moderate risk, it may be eligible for a de novo reclassification.
- If the test is done “in house,” in the designated laboratory only, for a patient sample that is sent to the laboratory from an outside physician’s office or medical facility, then the test can be potentially marketed under “home brew” guidelines (also known as laboratory developed tests) regulated under the Clinical Laboratory Improvement Amendments (CLIA).

**Figure 1: Regulatory Approval Process**

- **Class 1 (Low Risk)**: Exempt
- **Class 2 (Moderate Risk)**: Traditional 510(k)
- **Class 3 (High Risk)**: Premarket application (PMA)
- De novo 510(K) No predicate
- Device needs to demonstrate safety and effectiveness
- 510(k) review 90 days
- PMA review 180 days
- FDA Clearance
- FDA Approval
Clinical Laboratory Improvement Act 1988 (CLIA)

CLIA is an accreditation program under the US regulations for clinical laboratories, to establish “quality standards for all non-research laboratory testing performed on specimens derived from humans for the purpose of providing information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health.”

CLIA certification is based on three levels of test complexity - waived, moderate and high.

Waived tests must be simple and have insignificant risk of an erroneous result. Laboratories performing only waived tests are subject to minimal regulation, whilst moderate or high tests are governed by proficiency testing, quality assurance, quality control and inspections. IVD manufacturers should apply for CLIA categorization during the pre-market process. Point of care and self-test IVDs generally require a CLIA waiver.

EU Conformity Assessment Procedure

To obtain a CE mark in the EU, the manufacturer must ensure that the device meets the essential requirements of the IVD Directive by following the appropriate conformity assessment procedures according to IVD classification. Notified Bodies (NB) are licensed by the national regulators (Competent Authorities) to perform conformity assessment of medical devices including IVDs.

The manufacturer must register with one Competent Authority in a Member State, preferably the state where the place of business is registered. If the manufacturer does not have a registered place of business in a Member State and wish to place IVD in the European market then they should designate a person established in the community to act on manufacturer’s behalf as Authorized Representative.

For IVDs in the general (self-certified) category, a Declaration of Conformity can be prepared and supporting evidence documented. There is no Notified Body intervention but the products must be registered with the Competent Authority. For general IVDs the manufacturer self-declares conformity with the relevant essential requirements of the Directive.

For self-test devices, there is a requirement for the manufacturer to submit details of the device design to an independent certification organization known as a Notified Body. The Notified Body will assess the design of the device in terms of its suitability for non-professional users. Alternatively, manufacturers can opt to follow the routes for higher risk products.

IVDs for self-testing and those included in Annex II List A and B need the intervention of a Notified Body in the Conformity Assessment procedure before the device may be CE-marked and placed on the market.

For moderate and high risk IVDs (Annex II List A and B), the manufacturer’s quality management system must be fully audited by a Notified Body to demonstrate conformity with the requirements of the IVD Directive. For some products in List A of Annex II “Common Technical Specifications” (CTSs) have been developed to establish the minimum performance requirements of the device. Manufacturers must use CTSs, where established, to demonstrate conformity with the Directive. CTSs define appropriate performance evaluation and re-evaluation criteria, batch release criteria, reference methods and reference materials. In addition, products in List A of Annex II will require batch release by the Notified Body.
Performance Standard:

IVD performance is demonstrated through accuracy, repeatability, specificity, and sensitivity and defining limits of detection/quantification (Figure 2).

Figure 2:

Specific performance characteristics: Include, as appropriate, information such as accuracy, precision, specificity, and sensitivity. These should be related to a generally accepted method using biological specimens from normal and abnormal populations. Include a statement summarizing the data upon which the specific performance characteristics are based. Performance objectives should clearly state what is being measured and how this will be done. Performance end-points should be clearly linked to clinical claims and a statistical hypothesis provided with supporting sample size calculations. As with all clinical investigations, endpoints should be measurable, reproducible and standardized across investigational sites. Where a measurable endpoint is not possible, bias should be minimized.

A minimum of three investigational sites should be used, with multiple operators and a setting that reflects the intended setting for clinical use. Test operators should reflect intended users in terms of education and experience. Day to day variability and operator variability should be taken into account when considering intended sample type and testing matrix. Final versions of the device should be used according to the final instructions for use.
Software:
Software may be an accessory to an IVD and as such be registered as an IVD in its own right. Standalone software qualified as in vitro diagnostic medical devices is regulated according to Directive 98/79/EC. Software that is specifically intended by its manufacturer to be used together with an IVD medical device to enable that device to be used in accordance with its intended purpose falls under the scope of the IVD Directive and shall be treated as an IVD device in its own right. Examples: Analysis and interpretation of the optical density delivered by an ELISA reader, line or spot pattern of a blot.

About UL IVD Services
UL provides complete lifecycle services for IVD manufacturers seeking global regulatory approvals. We manage every facet of the global launch plan throughout your development continuum, from initial R&D and testing the product to conducting validation studies and clinical studies to final submission for low or medium to high risk IVD products.

Anticipated changes in the upcoming IVD Regulation:
An EU Regulation will replace the current Directive 79/98/EC, further encouraging a harmonized single market for IVDs and replacing the patchwork of national rules which transposed the IVD Directive. The new Regulation will cover all devices that are placed on the market from the moment it is applicable.

The expected changes in the Regulation can be divided into two areas: Firstly, ‘technical’, IVD-specific areas which cover the essential requirements, classification system, conformity assessment procedures and clinical evidence requirements. Secondly, features common to the medical devices sector (IVDs as well as other medical devices) such as the designation and monitoring of notified bodies, vigilance and market surveillance and its governance system.

A new classification system for devices is expected which would ‘upgrade’ many devices to a higher class of risk. The new Regulation is also likely to tighten up conformity assessment procedures and introduce new requirements for notified bodies. For many manufacturers this means a more stringent, time-intensive and costly set of requirements impacting the design and manufacturing of devices. Both new and already existing devices would need to comply with the requirements.

New clinical evidence requirements specific to the IVD sector are also expected at the level of the way a device works to provide a diagnosis. There would be additional requirements for clinical evidence, especially for new devices. This would help patients and laboratories by making the work of laboratories and health care professionals easier when selecting new tests.
References:


2. FDA To Exempt Some IVDs from 510(k) Clearance, IVD Technology, Published: March/April 2012, Volume 18, No. 2.

3. Centers for Medicare & Medicaid Services, Medicare Learning Network, Clinical Laboratory Improvement Amendments (CLIA), ICN #006270 May 2012 (http://www.ok.gov/health2/documents/MFS%20CLIAbrochure.eff.05.2012.pdf)

4. Sale and Supply of In Vitro Diagnostic Medical Devices, Sep 2011, MHRA, Bulletin 12


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