MEDTECH INSIGHT
CITELINE COMMERCIAL

24 Nov 2015 | **News**

New World Of Regulation Awaits IVD Companies In Europe From Coming Reforms

by

EU power players are currently negotiating vast changes to how in vitro diagnostics are regulated in Europe. The resulting system will involve a lot more external oversight than today for most IVDs. Here's a rundown of what to expect.

Currently in the European Union, the majority of in vitro diagnostics – some 80% to 90% – can be placed on the market without the need to involve an auditing organization. But if proposals now winding their way through EU policy halls become final, that dynamic will flip.

The proposed In Vitro Diagnostic Regulation (IVDR) that is close to being adopted will make it so some 80% to 90% of IVDs *will now be subjectto some level of auditing* by a third-party testing and certification body (notified body) before they can be placed on the European market.

As a result, the IVD industry will need to face up to some big changes, which will require significant new resources and extra expenditure in a market that is valued at around $12 billion.

"The IVD sector is about to undergo a quantum leap change in the depth of regulatory oversight," Sue Spencer, who heads IVD activities at the large notified body BSI, recently *told Clinica*. "The medical device sector has effectively had a series of five revisions with an associated increase in expectations and requirements; whereas the IVD sector will undergo all these changes at once."

EU policymakers have been working on the new regulation to replace the current In Vitro Diagnostics Directive (98/79 EC) for several years now, including a 2012 proposal by the European Commission, and counter-proposals by the Parliament and Council. The three bodies are currently involved in "trilogue" talks on a final package with adoption targeted sometime in the first half of 2016.

Significant Changes To Risk Classifications

The IVD Directive, adopted in 1998, is one of three EU medical device directives, along with the Active Implantable Medical Devices Directive (90/385/EEC) and the Medical Devices Directive (93/42/EEC). But the IVDD requirements are far less stringent than the other two based on a rationale that the products are not used on or in human subjects.

The level of involvement of notified bodies in an IVD or medical device file is linked to the level of risk of the product. Table 1, below, lists existing risk-based IVD categories, with examples, and the "conformity assessment" steps required to launch products in each category.

Table 1

Risk-Based Conformity Assessments – Current System

IN VIVO research

Classification	Examples	Conformity Assessment
General IVDs (low risk)	Cancer tests	Manufacturer self-certifies and affixes a CE mark after drawing up technical documentation, preparing a declaration of conformity with the "essential requirements"
Self-testing (medium risk)	Ovulation kits	Notified body is involved in review of design and labeling; otherwise, same as general IVDs
Annex II – List B (high risk)	PSA testing, rubella testing, self-test blood glucose monitors	The choice of either: • Notified body audits full quality assurance and reviews design; or • Notified body performs type examination audit plus either audit of production quality assurance system or product examination
Annex II- List A (high risks/subject to Common Technical Specifications)	Tests for HIV and blood groups	In addition to what is required for List B, the notified body must verify each product or batch of products and test them against the CTS requirements

Testing of conformity to the "essential requirements" of the directives by notified bodies is required for all but the lowest-risk medical devices under the Medical Devices Directive, it is restricted to a minority of IVDs under the IVD Directive. At present, most IVD companies can simply self-certify after ensuring they comply.

For the general category of IVDs, there is no need for clinical evidence, nor for performance studies. The manufacturer must simply put together technical documentation; ensure the manufacturing process follows quality assurance principles; and affix CE marking, once a firm is sure that conformity assessment procedures demonstrate compliance with relevant EU "essential requirements" (ERs).

For the remaining three categories – home-use self-testing diagnostics such as pregnancy tests, "List Bhigh-risk tests and "List A" high-risk tests – a notified body will be involved to some extent and the specific requirements will elevate with risk. For the most risky diagnostics in List A, so-called Common Technical Specifications (CTS) have been established to set more specific standards for certain product types.

But under the reforms currently being negotiated, the risk categories would be revised significantly to where most tests would require a notified body. The new risk categories and conformity assessment expectations proposed by the European Commission, and not opposed by the Parliament or the Council are laid out in Table 2.

Table 2

Expected Risk Categories And Conformity Assessments Under New IVDR

Notified body involvement is mandatory for Classes B, C and D

IN VIVO research

Risk Category	Definition	Conformity Assessment
Class A (lowest risk)	• Instruments and specimen receptacles	• Manufacturer draws up technical documentation, performs post-production review and self-certifies • Notified body is only involved in special cases – sterile devices, functional measuring and near-patient testing
Class B	• Devices which are controls without a quantitative or qualitative assigned value • Devices not covered by the other	• Requires full quality-assurance (QA) examination, with supplementary

	classification rules	requirements for self-testing and near-patient testing
Class C	• Screening for the selection of patients: companion diagnostics, devices intended to be used for disease staging, or cancer screening tests or diagnostics • Devices intended for self-testing generally classified as class C • Devices for blood glucose determinations and blood gases for near-patient testing; Note: other point-of-care tests are classified on a case-by-case basis. • To monitor levels of medicinal products, substances or biological components, when an erroneous result could lead to a decision resulting in a life-threatening situation	The choice of either: • Full QA and design dossier examination; or • "Type" testing coupled with product verification and production QA; And • Supplementary requirements for self-testing and near-patient testing
Class D (highest risk)	• Tests to diagnose a life-threatening, often incurable disease with high or undefined risk of propagation (e.g., HIV) • Tests for transmissible agents to assess transplantation/transfusion suitability (e.g., nvCJD) • Markers for the following blood group systems: ABO; Rhesus; Kell; Kidd; Duffy	The choice of either: • Full QA and design dossier examination; or • "Type" testing coupled with production QA, including batch verification

Wait, There's More…

The new risk classifications and conformity assessment requirements are not the only significant regulatory changes for IVD companies envisioned in the IVDR drafts. There are also proposals for a new "scrutiny" procedure for high-risk products, an enhanced focus on companion diagnostics, and new demands for clinical evidence, among others.

Scrutiny Procedure

Based on the proposals under negotiation, it is likely that an additional, more centralized process will be put into place allowing an EU-designated body to perform an extra review of notified body assessments for select, high-risk devices. (See (Also see "*EU Device Reform Proposal Adds More Government Scrutiny, But No FDA-Like Review Body*" - Medtech Insight, 1 Oct, 2012.).)

The European Commission has proposed that authorities should be informed at an early stage about high-risk IVDs subject to conformity assessment by the notified bodies. It proposes that the authorities should then be given the right, on scientifically valid grounds, to scrutinize the preliminary assessment conducted by notified bodies. In particular, the focus of such scrutiny would be on IVDs:

- for which no Common Technical Specifications exist;
- that are novel or for which a novel technology is being used;
- that are in categories with increased serious incident rates; or
- for which significant discrepancies in the conformity assessments by different notified bodies have been identified regarding substantially similar devices.

The European Parliament wants to go even further and have additional layers of review for the more risky IVDs. Meanwhile, the Council has its own proposal that would lessen the grasp of the Commission's proposal.

The three bodies *have yet to* directly address the details of the "scrutiny" proposals during the first four trilogue negotiation meetings.

Companion Diagnostics

Under the current IVD Directive, companion diagnostics fall under the general category of diagnostics and do not require notified-body oversight. Based on risks associated with tests driving drug therapy, the EU is tightening up requirements for companion diagnostics. The intention is for these products to be in the second highest IVD risk category for which a notified body will be involved in auditing the company and the products. The latest proposed definition of a companion diagnostic from the Council of the EU is more closely aligned with FDA's definition. (See box.)

EU Council’s Proposed Companion Diagnostic Definition

A companion diagnostic is a device that is essential for the safe and effective use of a corresponding medicinal product and is used:

- to identify patients who are most likely to benefit from the medicinal product; or
- to identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with the medicinal product; or
- to monitor response to treatment with the medicinal product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

The Commission's original definition reads that companion diagnostics are "specifically intended to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy."

The European Diagnostic Manufacturers Association (EDMA) is opposing the new Council definition, because it argues that the broad definition of companion diagnostics would result in a significant proportion of IVDs being unnecessarily categorized as companion diagnostics.

Clinical Evidence – A New And Demanding Factor

New clinical evidence requirements for IVDs are anticipated as well. Companies will be expected to provide more information on analytical performance, scientific validity and clinical performance as part of an overall clinical evidence package.

"The purpose of clinical performance studies is to establish or confirm aspects of device performance which cannot be determined by analytical performance studies, literature and/or previous experience gained by routine diagnostic testing," the European Commission states. "This information is used to demonstrate compliance with the relevant general safety and performance requirements with respect to clinical performance. When clinical performance studies are conducted, the data obtained shall be used in the performance evaluation process and be part of the clinical evidence for the device."

It is proposing that clinical performance studies be required for all IVDs except Class A – unless "duly justified." Further, under the proposal, the clinical evidence report, which must be included or fully referenced in the technical documentation, must contain:

- clinical performance data;
- analytical performance data; and
- information supporting the scientific validity of the analyte.

The Council of the EU, meanwhile, is proposing a revised definition of clinical evidence: "clinical data and performance evaluation results pertaining to a device of sufficient amount and quality to allow a qualified assessment of whether the device achieves the intended clinical benefit(s) and safety."

Likely Implementation Timeline

June 2015 – Council of the EU agrees on its position

2nd half of 2015 – Trilogue* discussions commence (October 13 – December 3, provisionally)

2016 – Adoption of IVDR, publication and entry into force

2021 – Full implementation

*European Commission, Council of the EU and European Parliament

EDMA is opposed to the Council's proposed changes in this context. "The entire terminology of the clinical evidence system has been revamped and unfortunately applied inconsistently, leading to a confusing text," according to the industry group.

The Council's approach to clinical evidence would lead to a significant additional burden for industry, EDMA says. It argues that "the risk is that such an approach would result in an insurmountable barrier to entry onto the market for many IVDs."

The IVDR proposal also introduces the potential for Common Technical Specifications for high risk, "Class D" IVDs and raises the prospects for additional requirements for "in-house," or laboratory-developed, tests.

Five-Year Transition Expected, But Don't Delay Preparation

With all of these changes on the table, IVD test makers are going to need time to adapt. The IVDR would not be enforced until three years after adoption at the earliest, but likely not until five years after, depending on the final trilogue agreement. The lengthy transition period is a factor of the extensive changes to existing procedures, and the major effects that these will have on manufacturers' practices.

In theory, five years should be sufficient as an adjustment period. But there are warnings from some within the EU IVD sector that even this much time will only be enough if the sector moves with a sense of urgency once the IVDR text is adopted and the relevant structures are in place.

"It is widely recognized that even with a five-year transition period manufacturers should not delay their preparations if they wish to avoid resource limitations," BSI's Spencer said.

- *For an expanded version of this story go to In Vivo, the premier strategic business resource for the biopharma, medtech, and diagnostics industries.*