Perspective: New European IVD Regulations—New Concepts for Market Authorizations and Product Launch Schedules

Planning for Efficiencies of Data, Resources, and Timelines
Introduction

On April 5, 2017, the European Council passed the new *In Vitro Diagnostics Regulations (IVDR)*, which will replace the current IVD Directive 98/79/EC (IVDD).\(^1\) For a significant number of products previously self-certified and therefore exempt from Notified Body (NB) review, there will now be a requirement for the technical and quality documentation to be submitted for NB review prior to product launch. The impact to IVD market authorizations and launch plans include stricter certifications for NBs, more detailed pre-market scrutiny and post-marketing surveillance, strengthened rules for high-risk IVDs, and increased transparency and traceability. The bottom line is that the EU IVD regulatory paradigm will shift from 80% of IVDs being CE marked by self-certification to only 20% self-certified, with the remaining 80% requiring NB prelaunch review of product documentation. This shift will drive IVD innovators to rethink their market sequencing and global commercialization strategies to reflect that post-IVDR, early commercialization in the EU over the US may no longer be the optimal choice.

Under the new regulation, 80% of IVDs will require Notified Body review.

Current EU Regulatory Landscape

Up to this point, the EU has overseen IVDs through country-specific adoption of the IVDD, which specifies required technical and quality documentation for the product to be maintained by the company. For about 80% of IVDs, companies could self-certify and CE-mark their products, indicating that the IVDD requirements had been met without oversight or review by an NB. Self-certification encompassed companion diagnostics and those IVDs not listed in IVDD Annex II. Among other information, self-certification documentation notably included:

- The Annex Classification
- The Technical File
- The Declaration of Conformity
- Quality System documentation

For the remaining 20% of IVDs, including the highest-risk diagnostic tests (eg, Annex II and/or self-testing IVDs), review of the technical and quality documentation and (in some scenarios) product testing by an NB was required.

Additionally, there were a few diagnostic products not subject to IVDD oversight at all, including assays developed and used in-house (eg, Laboratory Developed Tests [LDTs]) and algorithm software (covered by the product it supports).

Changes in the EU: Closer Alignment With the US Regulatory Landscape

Currently, FDA oversees IVDs and their ongoing performance in terms of regulatory classification, product code, performance, formal Quality System Regulation–compliant practices, and premarket submissions.

The evolution of the regulatory landscape for all types of IVDs is hard to predict during these fast-moving times, but the simplest aspect to forecast is the coming significant overlap of US FDA and EU oversight of IVDs. IVD innovators should welcome this new overlap, as it will tend to harmonize the development processes between the US and EU. This offers more opportunities for shared data across submissions and to streamline the process of bringing a regulated IVD to the global market. The figure below demonstrates the future alignment of EU IVDR and US FDA regulations for IVDs.

The coming US-EU regulatory overlap should allow a welcome harmonization of product development processes.

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**US FDA**

- CFR Numbers and Product Codes
- Analytical and Clinical Data
- Algorithm Software
- Class II or III
- Quality System Regulation (21 CFR 820)
- US FDA
- Premarket Review
- LDTs Under FDA Enforcement Discretion

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**EU**

- Regulation Classification
- Performance
- CDx Classification Based on Risk
- Quality Systems
- Premarket Review
- EU Notified Body
- LDTs Not Part of IVDR

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**Commonalities 2017**

- A, B, C, D
- Assay Technical File Including:
  - Analytical and Clinical Data
  - Algorithm Software
- ISO 13485
- EU Notified Body
The major paradigm shift in EU IVD oversight becomes critical for IVD innovators in terms of business launch plans and timelines. Starting in 2022 (five years after publication of the IVDR), the typical business approach of initial launch in the EU for early commercialization will no longer be the default preferred option. At that time, for most IVDs the EU process and timelines will be similar to those of US FDA. The difference will be that IVDs with CE marks under the current IVDD will only be valid for up to 2 to 3 years after full application of the IVDR. Companies will be required to submit new CE marking applications to NB under the IVDR to remain on the market.

Although the transition period for full EU application of the IVDR is 5 years after publication, submission reviews can start once the IVDR has been published, so IVD developers should be prepared to navigate the new EU regulatory landscape as early as late 2017. And with current CE marking “expiring” within 2 to 3 years of application of the IVDR, companies need to start planning now to avoid market interruption.

Action Steps for New Product Launches and Current Product Continuation Planning

To remain on the market, products with current CE marks will need to reapply for Notified Body approval.
Action Steps for New Product Launches and Current Product Continuation Planning (continued)

Below are some suggestions for preparing for the IVDR:

1. Review and prioritize the assays in the test portfolio to be submitted for review, based on business needs and technical criteria of the assays.

2. Identify an NB for the future review process in anticipation of limited numbers of EU-certified NBs, and a logjam of premarket submissions for currently marketed assays.

3. Prepare a list of the required analytical and clinical study data needed for a submission to an NB for each product.

4. Identify similarities in requirements across US FDA and EU IVDR to maximize leverage of the previously completed work and to minimize duplicative efforts going forward. Critical areas in which to seek similarities include:
   - Assay Design
     - Intended Use and Indications for Use
     - Documentation: regulatory requirements versus good quality practices
   - Assay Manufacturing
     - Documentation: regulatory requirements versus good manufacturing practices
   - Assay Performance Validation
     - Population claims
     - Protocols, data analysis plan, and acceptance criteria
     - Validation reports

5. Make the hard decisions on assay discontinuation based on availability and/or quality of existing data, level of effort needed for new studies, and impact on business plans.
Once the EU IVDR is fully implemented, initial IVD launches in the EU may no longer be the norm. All product development and launch timelines will be gated by US FDA and EU NB review, taking into account: 1) the time needed to prepare a formal NB submission that contains the required documents; 2) the rate-limiting number of certified NBs; and 3) the likely possibility of large review backlogs caused by the large number of IVDs requiring NB review towards the end of the 5-year period.

Companies should expect large NB review backlogs and possible delays toward the end of the IVDR implementation period.

Executing a set of internal preparation steps in the 5 years between the EU IVDR publication and its full application will help IVD companies pave an efficient and timely path for their products to comply with the new requirements. Moreover, beginning the process with currently marketed IVDs will provide a template and tested process for future IVDs that the company might bring to the EU market. And with the significant crossover of requirements between the EU IVDR and US FDA regulation, study designs and documentation can be optimized to meet the demands of both regulatory authorities.

With careful planning, companies can benefit from shared study designs and documentation to meet the demands of both regulatory authorities.

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Judi has worked in the medical products regulatory submissions and approvals, quality, and clinical trial areas for over 30 years. In her role, she oversees a team that provides a full range of IVD and blood screening assay services including regulatory strategy, analytical and clinical study designs, protocol development, and all FDA premarket and postmarket submissions.