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Potential impact of IVDR on diagnostic testing in Europe
What are the implications for the pharmaceutical industry?

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Introduction to IVDR

All new In Vitro Diagnostics (IVDs) placed on the market after May 2022 have to comply with the European Union In Vitro Diagnostics Regulation[1] or IVDR. All existing CE certified devices must comply with the IVDR by 26 May 2025 or upon certificate expiry. The transition period for existing IVDs depends on their risk class; for IVDD self-declared devices this is 26 May 2025 for Class D devices, 26 May 2026 for Class C devices and to 26 May 2027 for Class B and A sterile devices.

By 27 May 2027, all devices must comply with IVDR.* There is no doubt that this regulation is going to change the landscape of diagnostic provision in the European Union. But what are the implications to the pharmaceutical industry as they seek the optimal solution to accompany their targeted medicines both in development and once launched into the European healthcare system?

* Note: Recent proposals from the EU commission have recommending the postponing of the final transition dates by approx. 1 year. To be ratified by EU Member States. See: Press Release

IVDR – what is new?

Under the previous European Directive, (IVDD), only a small percentage of tests were certified by a Notified Body, with the majority being self certified requiring no Notified Body involvement. However, under IVDR the vast majority (80%) will now need certification by a Notified Body. Furthermore, the certification process includes new classifications for devices, more stringent technical documentation (GSPR), stricter requirements for analytical & clinical evidence and new requirements for scientific evidence, Unique Device Identification (UDI) numbers and post market surveillance requirements.

Although the IVDR was introduced in May 2022, as mentioned above, existing assays can be transitioned and used for interim periods allowing companies and laboratories time to prepare for what is seen as a radical change in diagnostic regulation. The transition periods will also allow the pharmaceutical industry to take stock and consider what they need to do to be ready to meet the needs of Europe, as well as the ongoing needs of the USA and the FDA. Newly developed assays as from May 2022 will need to meet the above mentioned more stringent IVDR requirements and appraisal by a Notified Body, especially if they are utilised as Companion Diagnostics, which are classified as Class C under the new classification system.

Challenges in the implementation of IVDR

One of the challenges that led to the delay in the regulation going forward in 2022 was the backlog of assays seeking approval and the inevitable inexperience of both companies and regulators in navigating the new process. This has resulted in extended transition periods and sell off clauses allowing assays already approved under IVDD to be utilised in the interim, provided certain post market requirements are met. However, changes to such assays or indeed development of new assays need to meet full IVDR requirements post May 2022.

Another challenge is the delay in the full implementation of EUDAMED, the European Database on Medical Devices. This is the IT system being developed by the European Commission as an integral part of IVDR implementation. The system integrates six modules to collate and process information on medical devices and manufacturers:

- **Actor registration.**
- **Unique Device Identification (UDI) and device registration.**
- **Notified Bodies and certificates.**
- **Clinical investigations and performance studies.**
- **Vigilance and post-market surveillance.**
- **Market surveillance.**

Unfortunately, the Clinical investigations and performance studies module is still not functional (as of January 2024). As a result Clinical Performance Study Applications and corresponding Ethics Committee reviews must be submitted to each Competent Authority and ethics board necessitating co-ordination of these across multiple jurisdictions in the EU for trials recruiting across multiple EU countries. This can add significantly to trial set up time for interventional and registrational IVD trials in the EU.

> *"Another challenge is the delay in the full implementation of EUDAMED, the European Database on Medical Devices"*

Background – Companion Diagnostics

Historically, the USA has been the market where Companion Diagnostics (CDx)[2] has been an essential part of drug development, with parallel drug and device submissions, both receiving intense scrutiny from the FDA's Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) respectively. So, the selection of a diagnostic development partner by pharmaceutical companies has always been a carefully managed process, with the potential partners capabilities, knowledge and experience of the Companion Diagnostic regulatory process being key to their selection and ultimate market approval.

In Europe, previously under the In Vitro Diagnostics Directive (IVDD), the assay or test developed by the diagnostic partner would acquire approval as a CE-IVD test[3], but with far less scrutiny than the US process. Also, it was often the case that the selected CE-IVD test would not be favoured by European labs or physicians in lieu of local Lab Develop Tests (LDTs). This rarely slowed down adoption of the biomarker in question, as testing was possible with LDTs that were readily available and would have been developed, validated, and used routinely by hospital labs. Typically, these LDTs would serve patients well, with External Quality Assurance (EQA)[4] programmes policing the accuracy of their results and ensuring high quality standards. In many cases in the early days of diagnostic provision there were more EQA failures with LDTs, but as assessment programmes were repeated the mistakes were eradicated and quality subsequently improved[5].

The evolving landscape of approved tests vs LDTs

What is often forgotten by a pharma company when they are launching a medicine with a CDx, is the low uptake of the actual co-developed and subsequently approved CDx assay, due to the availability of similar local Lab Developed Tests (LDTs). It has not been mandatory for the approved test to be used by a physician or laboratory. In fact, in the case of a point mutation being detected by a simple CDx PCR type test, it might be far more convenient for the physician, lab and patient for a Next Generation Sequencing (NGS) panel, assessing multiple possible mutations to be used. So, historically LDTs have a similar high share of the testing landscape for each diagnostic (estimated up to 80%).

Will Europe still have LDTs with IVDR?

Additionally, European testing is rarely centralised, and the ethos has always been for local testing to take place in relatively small local laboratories. This has worked well for local routine cancer diagnostic testing, speeding up turnaround times and maintaining the relationship between pathologist and physician. It has meant that NGS testing is more likely on smaller panels and instruments as the volumes of samples are smaller compared to the USA. For example labs would often develop a customised panel to meet their needs, and simpler PCR or Immuno Histochemistry (IHC) tests were easy to provide in these labs as well. So, consequently as the LDT assays ensured the local labs could provide the test most effectively, most companies had little or no need to get CE-IVD approval as it was not necessary for these labs to adopt the approved assay.

Initial reluctance by labs to get ready for IVDR was based on the simple principle of “well it never mattered before so I doubt it will in the future” and an assumption that the healthcare system would support them doing what they had always done. However, the EU had suffered at the hands of poor device provision and had been hounded to tighten their regulations. Thus, as delineated in Article 5(5) of the IVDR, there is now a more stringent framework for the manufacture and use of in vitro diagnostic LDTs, especially regarding the control of their safety and performance.

This is highlighted in the preamble of the IVDR, where point 28 states: "To ensure the safety of health protection, the rules governing IVD medical devices, manufactured and used within a single health institution only, should be clarified and strengthened."

The IVDR 'in house' requirements for LDTs will, as a result, require a higher bar of regulatory compliance before they will be permitted, including post-approval commitments, thereby turning all labs with LDTs into de facto "device manufacturers". Consequently, all but the best financed labs will not have the resources to validate their LDTs and perform post market commitments to meet this requirement. So it would be likely that LDTs all but disappear in the majority of labs over the coming years, especially for Companion diagnostics.

A game changer

So now labs in Europe are going to be forced to look at every diagnostic they provide and decide their course of action to provide that test:

1. **Adopt an IVDR approved test.**
2. **Get IVDR approval for their own test.**
3. **Meet the Health Institution definition and meet the requirements of Article 5(5).**
4. **Stop testing for the biomarker and send out to another laboratory.**

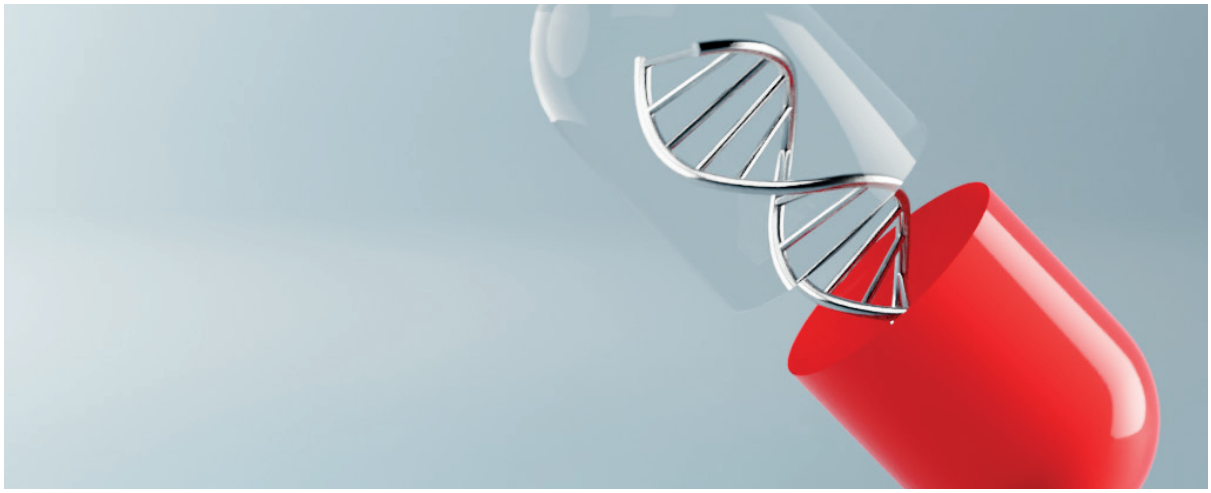
So now with IVDR, IVD diagnostic companies will have an incentive to seek IVDR approval for their assays, as there is a more level playing field with respect to the IVDR regulatory requirements for any competing LDT type assays and potentially as a result less competition in the market from these types of assays.

What does pharma need to do?

On the face of it there might be a "space race" for diagnostic companies to get their assay IVDR approved, and Pharma can sit back and let them do their work for them. This certainly is likely for well-established tests where the market is mature. However, one challenge will be where the CDx approved assay is unlikely to be adopted by labs, as it is a centralised lab test where testing is preferred locally, or it is a kit-based test that is run on a platform that few labs might have.

If pharma wants rapid adoption of a test (and they always do) they are going to need to consider the flexibility of their partner to meet the needs of multiple platforms, labs and even technologies. Having a test run on one company's platform which has a large share of labs is good, but there will always be important labs that will not be able to access the platform.

As a result, pharma might look to partners who can offer test solutions to as many labs as possible, even a combination of PCR and NGS approved tests on a range of different platforms from multiple platform providers. The ability to flex to alternative sample types is a growing need and in a more regulated environment will pose a new challenge with further pressure on those precious samples.



A recent case study was provision of HRD testing in Europe, where the CDx for AstraZeneca was the Myriad Genetics myChoice CDx[6], but at the time Myriad was well established in the US and had a low usage in Europe with a historical reluctance for physicians and labs to send samples outside of their country for testing. Two alternative tests were developed for the EU[7,8] but the option with greater flexibility has been the test most utilised. How many HRD LDTs will result will be interesting to observe, with development costs likely to be high.

The other key question is whether the pharmaceutical industry will develop parallel diagnostics for Europe and the US or whether the US remains the priority with additional partners potentially being added at launch.

Alternatively, there is an opportunity for a new set of companies with greater flexibility to serve the needs of multiple countries, technologies, and regulators to come to the fore. Leaving other players to focus on platform development and other products. It will be unlikely that platform selling companies will develop alternative assays for their competitor's platform.

Summary

The implementation of IVDR will undoubtedly improve the standard of diagnostic devices in Europe, that said, it will bring challenges for both Diagnostic companies, testing laboratories and the Pharma industry.

One solution for Pharma, to maximise test availability for their biomarker of interest, is to work with a diagnostic partner that can develop multiple solutions to enable broad adoption by the testing labs in Europe as well as serving the needs of the USA and the rest of the world.

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IVDR – Almac Regulatory Support

Almac can give Pharma partners up to date guidance and support for your biomarker programmes around IVDR and compliance with the new regulations for Europe.

Almac Diagnostic Services has updated all CTA and CDx processes to be compliant with the new IVDR. We have ensured any legacy devices CE marked under the IVDD are maintained in such a manner as to be available throughout the transition period to allow trials to continue seamlessly despite changes from the previous directive to the IVDR.

Find out more about our Regulatory Support Services here:

https://www.almacgroup.com/diagnostics/supporting-services/regulatory-and-qualityproficiency/

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