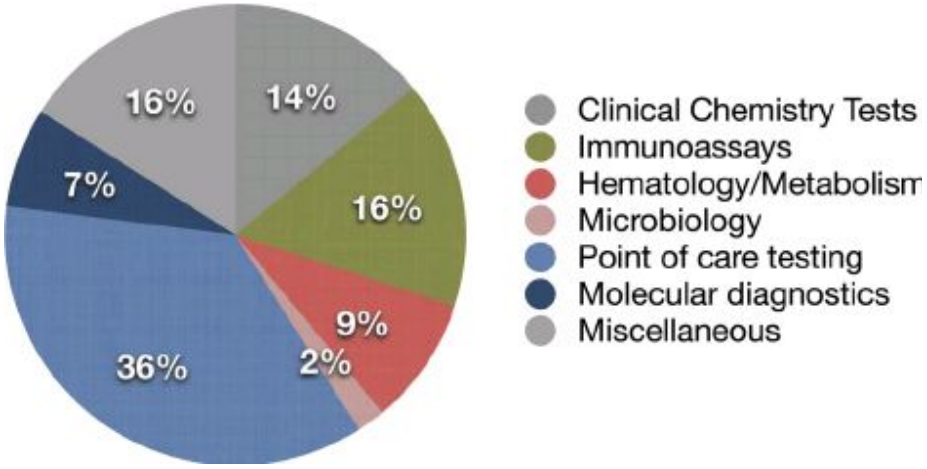
The in-vitro diagnostics regulation (IVDR): From oversight to overhead

The increasing expectation for early and accurate disease diagnosis along with the growing possibilities in personalized medicine has fueled the demand for in-vitro diagnostic medical devices (IVDs). These devices include laboratory or point-of-care devices, kits and reagents as well as other accessories, which are used to perform diagnostic tests on human samples. The global IVD market is estimated EUR 58 billion globally and is expected to reach EUR 75 billion by 2023, with Europe holding around one-third of this market.

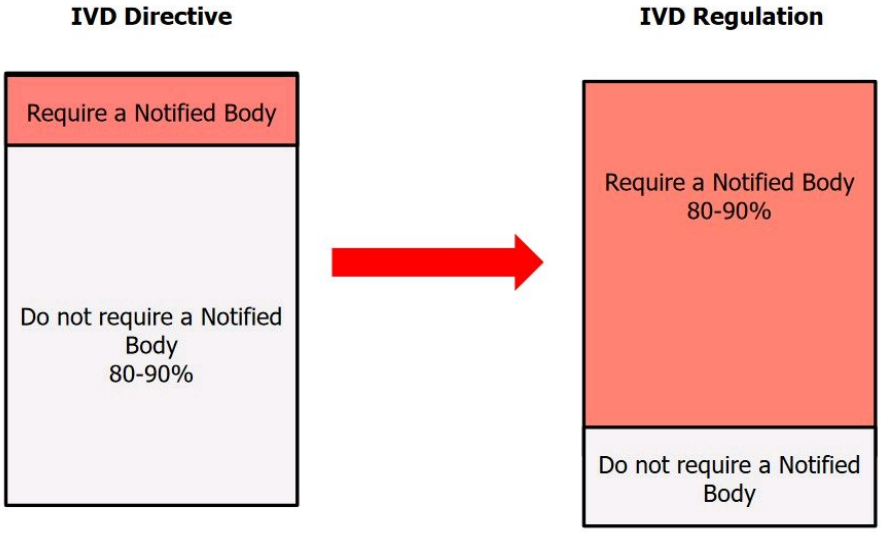


Source: Lab on a Chip

In recent months, many articles have been published on the coming Medical Device Regulation (MDR), however, few have zoomed in on the new in-vitro diagnostics regulation (IVDR). For this reason, this article will focus on the IVDR and discuss the key changes for IVD companies.

The regulatory framework

Traditionally, IVDs have been subject to little regulation when compared to medical devices or pharmaceuticals. Under the now phasing out in-vitro diagnostic directive (IVDD) almost 90% of IVDs were able to self-certify, similar to Class I medical devices. With the recent change in legislation for medical devices (read our MDR article), the IVD legislation has also been overhauled. In case you missed it: the IVDR came into force in May 2017 and companies are given a transition time of five years, up to 26 May 2022, to meet the requirements of the IVDR. Similar to the MDR, the IVDR means reclassification and reregistration of all products currently on the market. While the MDR is a step up for medical device companies, the IVDR is a true quantum leap in regulatory burden for IVD companies.



Source: BSI Group

The IVDR has been written with the intention to harmonize regulations across medical devices (MDR). Therefore, we should expect more clinical evaluation throughout the entire device lifecycle rather than on registration alone. Below we will cover three main ways the IVDR will impact IVD companies.

1. Wider scope of regulated IVDs

What products are considered IVDs? One of the major criticisms of the IVDD was that it did not cover new technological trends such as genetic testing or tests being offered over the internet. The IVDR now explicitly addresses these. Its scope is expanded to cover:

- Disease predisposition testing, such as neonatal screening for early recognition of treatable disorders. Preamble 10 and definition 2 have been written to include such tests.

- Companion diagnostics predicting treatment response to a particular medication. For example, a genetic test to differentiate cancer types or an IVD for a specific metabolic biomarker to determine the underlying cause of high cholesterol. See definition 7.

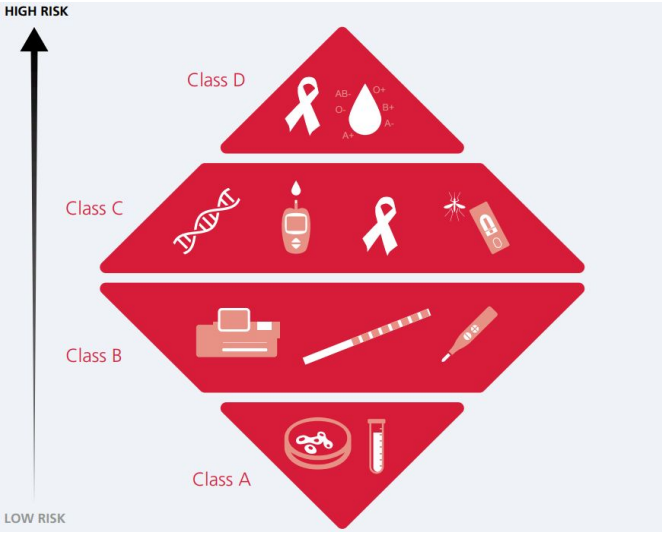
- Software: Definition 17 states that when software is developed with the purpose of diagnosis based on human samples (as defined in Definition 2) it is considered an IVD. This could have implications for medical app developers, currently not captured under IVD legislation. Note however, that software developed for diagnosis without using samples, such as assisting a doctor in decision making, is not considered an IVD but could still be considered a medical device.

- Non-EU distance sales: Non-EU companies offering a diagnostic tests/kits over the internet to EU citizens, even when the actual test is performed in a non-EU laboratory, must comply to the same regulations as EU companies.

If your company develops any tests that fall into these newly included fields, make sure you are up to date with what is expected of you.

2. Rigorous change in the way IVDs are classified

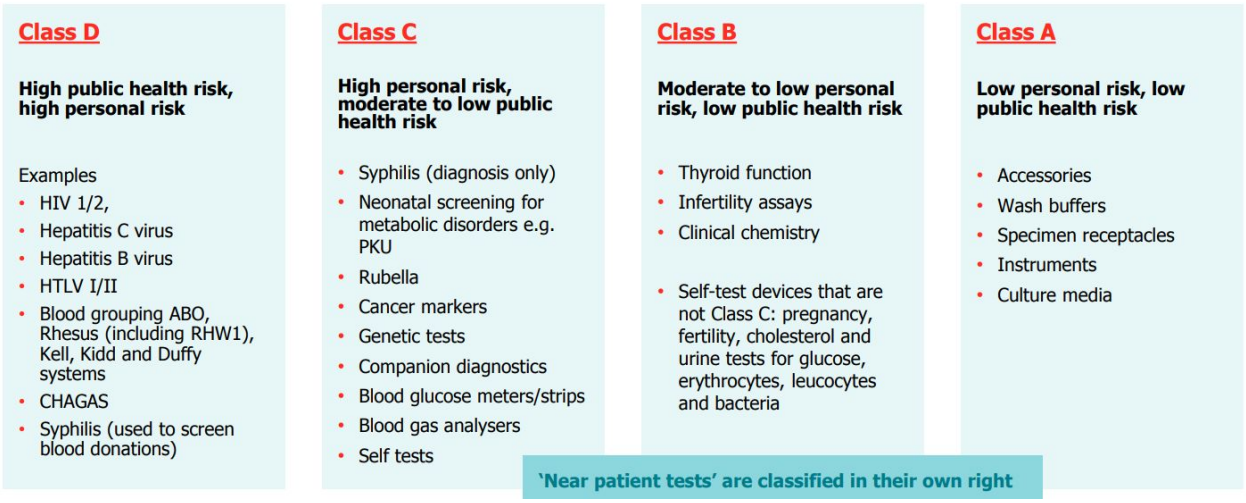
IVD classification under the IVDD was highly criticised for lacking a scientific basis and not allowing for new technologies. IVDs not listed explicitly under Annex II were able to self certify without Notified Body involvement. These tests made up the lionshare of the industry.



Source: Medtech Europe

The IVDR has adopted a risk based classification system, which in many ways, is similar to the medical device regulation. Any class but Class A now requires Notified body involvement, which is enormous increase in regulatory overhead.The IVDR identifies the following four risk classes:

- Class A, including reagents and receptacles, may continue to self certify;
- Class B, including pregnancy tests and infertility assays, require a quality management system (QMS). Notified bodies may audit the product's technical file on-site;
- Class C, including infectious disease testing, genetic testing and companion diagnostics, require a QMS and a full review of the technical file by the notified body;
- Class D, including blood screening and high risk disease tests, has similar requirements to Class C, and additionally requires verification of every batch by an external laboratory.



Source: BSI Group

Tests developed in-house by a health institution also need to be classified under the new regulation, including a self-declaration that the general safety and performance requirements are being met. This includes non-commercial and academic institutes under the regulation.

The new classification system means that manufacturers, including non-commercial institutes, need to review their products on the market and gather the evidence required to support conformity of their IVDs.

3. More stringent clinical evidence for IVDs

IVDs are distinct from medical devices, as they never come into direct contact with the patient. IVDs do, however, have an impact on treatment decisions which could be life saving so it is understandable that they require some level of clinical evidence for IVDs. The IVDD was very light on this and did not mention `clinical evidence` as a requirement. This has changed under the IVDR (definition 36-62), with the new requirements including:

- Scientific validity. What is the meaning of the result you read from a test? For example, measuring high glucose in a diabetic patient might not be valuable, as insulin levels may be needed to control for it;

- Analytical performance. What is the accuracy of the measurements in terms of sensitivity and specificity? This determines the certainty with which a test can make a differential diagnosis;
- Clinical performance. How does the IVD perform under different conditions? Does it work in the setting where it is meant to be used? An HIV test might perform differently in a cold climate than in a hot climate, which impacts its clinical usefulness.

Under the IVDR clinical data will need to be collected not only during registration, but also once it is on the market in the form of post-market surveillance. The regulatory change means that companies need to gather clinical data on an IVD to ensure it meets the listed clinical benefits and safety. Many of the manufacturers however don't have access to clinical data for existing products, making it an especially difficult challenge for legacy data/IVD devices.

Conclusion

Although the IVDD was highly criticised for a lack of oversight, the IVDR is more than a simple step up for the industry. Of course, clinical evidence will help physicians in making decisions on what diagnostics to run but under the new requirements, it is likely that large numbers of diagnostic tests will disappear or never reach the market because registration is too costly. While legislators do a good job of ensuring no life threatening IVDs enter the clinic, they may well have forgotten the opportunity cost.