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Your Expert

A Quality & Regulatory perspective on IVDR with Yourgene's Head of QA/RA

Yourgene Health

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In this edition of Your Expert, Yourgene's Head of Quality Assurance and Regulatory Affairs (QA/RA) **Claire Ryan** shines a light on the European Union In Vitro Diagnostics Regulation 2017/746 (EU IVDR) to de-mystify some of the remaining questions around the changes, what it means for Yourgene Health and the impact on their current IVD users.

Claire Ryan - Head of Quality and Regulatory Affairs

Claire has been the Head of Quality and Regulatory Affairs (QA/RA) at Yourgene Health since May 2022. Claire brings with her over 25 years' experience in Regulatory and Quality, having worked in both Medical Devices and IVD industries. Claire has expertise in CE marking and the IVDR, as well as extensive knowledge of the FDA and Health Canada regulations, and registrations requirements worldwide.

What is IVDR and what is its purpose?

IVDR entered into force in 2017 and expanded upon IVD Directive 98/79/EC (IVDD) requirements, which have been in effect since 1998. The aim of the regulations is ultimately to improve patient safety by setting tighter and broader requirements for the quality, performance and safety of IVD products. Obviously, this largely falls to the manufacturers to provide sufficient evidence, but there are also implications for consumers too.

Originally, completion was projected for May 2022, but several complicating factors including the COVID-19 pandemic and limited capacity of approved notified bodies slowed the uptake and adoption of IVDR.

In January 2022, the European Commission published an extension to the transition timelines but the date of application remained the same . This extension to the transition timelines gives everyone a little more time to become compliant, but we don't expect that this will be extended further.

The length of the new transitional periods depends on the risk class of the device and whether a notified body has previously been involved under the IVDD. The updated IVDR timelines are as follows:-

- Devices which are Class A non-sterile – including instruments, buffers, accessories without critical characteristics, general culture media etc. – must have CE-marking under the IVDR from the date of application (26 May 2022) in order to be placed on the market
- Devices which are IVDR Class B or Class A sterile: the transitional period ends on 26 May 2027
- Devices which are IVDR Class C: the transitional period ends on 26 May 2026
- Devices which are IVDR Class D or devices which have still-valid IVDD Notified Body certification: the transitional period ends on 26 May 2025
- 'New' devices will need CE-marking under the IVDR after the date of application. This includes any device which does not have its EC Declaration drawn up under the IVDD before the IVDR date of application of 26 May 2022

Note: Devices which have legally been placed on the market but have not yet reached the final user, can continue to be sold off without a deadline.

What will be some of the biggest impacts to users under IVDR?

IVDR is very prescriptive and prohibits IVD off-label use. This includes devices being used outside of the scope of their intended use, and it is also very clear that devices must not be used off-protocol.

It further prohibits Research Use Only (RUO) products being used for clinical purposes, as well as regulating more stringently in-house testing, also known as "home-brew" testing, or Laboratory Developed Tests (LDTs).

As long as users have an IVDR-certified product validated in their laboratory by the transition deadline and it is being used appropriately as advised by the manufacturer, there will be no adverse impact on their ability to perform diagnostic testing.

What is meant by in-house testing?

There is no definition within the IVDR for LDTs, unlike in the USA by the Food and Drug Administration (FDA). The IVDR calls LDTs *"devices manufactured and used only within health institutions established in the Union".*

There are two distinct types of in-house tests:

1. Tests developed by and conducted at a health institution (for example, a biopsy tissue sample). A health institution is an organisation whose primary purpose is the care or treatment of patients or the promotion of public health, and while the institution is placing an IVD "into service," it is not placing the IVD "on the (EU) market." IVDR Article 5 describes the specific requirements for these health institutions.

2. Testing services **where a sample is sent to a lab and a result is sent back (for example, a commercial genetic test using a saliva sample).** Testing services are covered under IVDR Article 6 regarding Distance Sales and are treated the same as if the IVD was sold commercially (placed on the market).

It should be noted that medical laboratories provide patients or the physicians treating them with medical information for a diagnosis. That is why medical laboratories can be considered health facilities according to the IVDR definition.

Is all in-house testing prohibited under IVDR?

No. There are some exceptions which are collated under the Article 5 (5) exemption. For an health institution to claim an exemption against Article 5:

- The health institution must justify in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market (i.e that no alternative CE-marked device is available on the market)
- The device must not be shared outside of the Health Institution
- The device cannot be made on an industrial scale
- Manufacture must occur under an appropriate Quality Management System (QMS), within a laboratory which is compliant with standard EN ISO 15189 (or equivalent national accreditation scheme)
- The device must meet the general safety and performance (GSP) requirements set out in Annex I of the IVDR, which the health institution shall make publicly available
- Sufficient documentation to demonstrate compliance of manufacturing facility, manufacturing process, design/performance data and intended purpose must be available
- Experience from clinical use must be regularly reviewed and corrective action taken if necessary

The laboratory who continues to use an in-house test effectively adopts the role of the manufacturer of the test, and so must demonstrate and declare compliance with the IVDR.

With the new amendment, the application of certain requirements for devices manufactured and used in the same health institution (so-called 'in-house devices') is delayed by two years until May 2024 (all provisions of Article 5(5) except point (d) - the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market. If the health institution proves that an equivalent device is not available on the market, the transitional period will end in May 2028 (full Article 5(5)).

The European Commission and the MDCG (Medical Device Coordination Group of the EU Medical Device Authorities) have published MDCG 2023-1: Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746. This document provides guidance on the application of some of these rules. It is written for healthcare professionals and researchers of health institutions aiming to design, manufacture, modify and use in-house devices.

So, in short, continued use of an "in house test" *is* allowable under IVDR. However, having had first-hand experience of preparing and submitting products for certification within a commercial manufacturing organisation, I can attest to how onerous a task it is to compile the required technical documentation and demonstrate compliance to all the other requirements which go above and beyond those laid out in the old IVD Directive.

How will compliance be enforced?

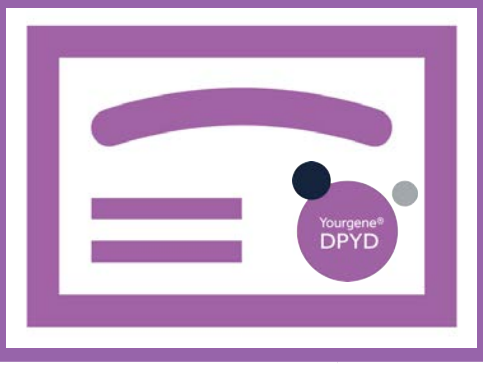
Whilst still in the early stages, compliance is expected to be monitored by individual member state competent authorities and laboratory inspectors. We expect that any penalties for non-compliance will also be set by individual member states.
Recent legislation published in Italy[1] indicates that financial penalties may extend into hundreds of thousands of euros per violation of the IVDR. Whilst not certain, it is expected that other member states may take this as a precedent and implement similar penalties of the same magnitude.

What does IVDR mean to Yourgene Health?

Yourgene Health's devices fall into either risk Class A or risk Class C. As with any major change in regulations, we anticipated that there would likely be significant difficulties getting the entire market compliant in time. When you see how few notified bodies there are, and the sheer volume of devices which would need to be assessed, it was always likely to take a lot of time and considerable resource.

Knowing how vital our products are in allowing our users to keep providing decisions which directly impact patient care, Yourgene Health committed early to an internal programme of works dedicated to getting our products transitioned, allowing our users to be ready in good time ahead of the final deadline.

We plan to CE-mark our Class A non-sterile products in accordance with IVDR in 2024. For now, our Class C devices retain their legacy IVD status and can be kept on the market as IVDs under the directive until May 2026. We have already agreed and committed to a schedule of IVDR product assessment for our Class C devices with our notified body, BSI.



Product Name	Part Code
Yourgene® DPYD (IVDR)	ONDYDB1

Yourgene DPYD genotyping assay receives IVDR certification!

This approach has really paid off, and we are thrilled to be able to say that Yourgene Health have the one of the first IVDR Kits for the rapid detection of the 6 clinically relevant variants in the dihydropyrimidine dehydrogenase (DPD) enzyme available on the market.

A product with IVDR certification enables clinician and patient confidence in a superior high quality test - *where accuracy matters*

What does the future of IVDR hold for Yourgene Health?

The Yourgene® DPYD Kit is just the first of many products for which we are seeking IVDR certification. Now that we have been successful in our very first submitted product, we confidently expect that our other devices will also be approved.
IVDR Announcements will be made on a regular basis, should you wish to be kept up to date, email dpyd@yourgenehealth.com to opt-in to receive updates.

Scan the QR code to view Yourgene's IVDR certification and IVDR timeline

About YOURGENE HEALTH

Yourgene Health is an international molecular diagnostics group which develops integrated genomic technologies and services *enabling genomic medicine*

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