IVDR compliance

# Making the transition to the *In Vitro* Diagnostic Regulation

## Introduction

Enforcement of the *In Vitro* Diagnostic Regulation (IVDR) will begin on May 26, 2022, and many hospital laboratories, independent diagnostic laboratories, and commercial manufacturers still have questions about navigating the IVDR transition. Under the new regulation, developers and manufacturers of *in vitro* diagnostic (IVD) products will be required to register most IVD assays and some in-house tests (IHTs) and assays for CE marking, including quantitative PCR (qPCR) and Sanger sequencing–based tests. Implementation of the **IVDR will benefit patients, diagnostic laboratories, and IVD manufacturers**. The IVDR sets higher standards for quality and safety than the *In Vitro* Diagnostic Directive (IVDD), and tighter post-market surveillance will help ensure that IVD products remain compliant throughout their life cycles (**news-medical.net**). The IVDR will also improve transparency throughout the supply chain by clearly defining the roles and responsibilities of manufacturers, distributors, importers, and authorized representatives.

However, diagnostic laboratories and IVD manufacturers who want to register their products will face a number of challenges. Manufacturers will have to demonstrate that their IVD assays meet strict new standards for analytical and clinical performance. Existing IVD tests, instruments, and in-house assays will not be grandfathered in under the IVDR, and it is possible that many IVD and IHT manufacturers will be unable to transition existing products to comply with the new regulation. This white paper provides an overview of how the IVDR will impact diagnostic laboratories and IVD manufacturers and describe the services and support Thermo Fisher Scientific offers to help them successfully transition to IVDR.

## What are the biggest differences between the IVDR and the IVDD?

The most significant differences between the IVDR and the IVDD involve device classification, technical documentation requirements, IHT registration, and the use of legacy data. The roles of the supply chain and businesses that import or export goods into or out of the European Union (EU) are also clearly defined in the IVDR, so contracts and agreements between business partners will need to be updated.

### Device classification

Manufacturers were allowed to self-certify approximately 80% of IVDs under the IVDD, and the products were classified as general IVDs. IVDD classification is based on a specific list of high-risk devices compiled in 1997, and new technologies have generally been considered low-risk regardless of actual risk. Under the IVDR, **only about 20% of IVD products will qualify for self-certification**. The IVDR moves device classification to a risk-based system that will apply to existing and future technologies, and they will now fall into one of four categories based on risk. Class A devices will fall into the lowest risk category, while Class D devices will be placed in the highest risk category. The IVDR also defines IVD products more broadly than the IVDD and will extend to genomic devices, companion diagnostics, personalized medicine products, and software.

### Technical documentation

Under the IVDR, technical documentation for most IVD products will require review by a notified body before the CE mark is issued. Technical documentation for IVD products must establish their scientific merits, analytical performance parameters, and clinical performance. In addition, notified bodies will oversee documentation throughout the life cycles of most IVD products.

### IHTs and in-house assays (IHAs)

Diagnostic laboratories who develop tests for their own use or who use commercial kits off label are creating IHTs and IHAs. While IHTs and IHAs will have to satisfy some additional requirements, they will be exempt from most elements of the IVDR under article 5. **IVDR enforcement for IHTs and IHAs will occur on a staggered schedule** that extends beyond May 2022. While CE-IVD tests will be given preference under the IVDR, laboratories can still develop their own tests. However, they must be able to justify not using commercially available CE-IVD tests to register IHTs and IHAs when enforcement begins in May 2028.

### Legacy data

Providing legacy data for products that went to market under the IVDD may not be sufficient under the IVDR, so IVD manufacturers may be required to perform additional studies and submit new data.

## What is Thermo Fisher doing to support the IVDR transition?

**Thermo Fisher Scientific** is fully committed to the development of CE-IVD devices that will comply with IVDR requirements, and we can help you quickly **navigate the complexities of the IVDR transition**. We offer **performance verification and instrument qualification services** to provide you with clarity and confidence. We can also provide IHT and IHA developers with **a complete tool kit for molecular diagnostic (MDx) assay development**, and we can assist you in selecting technologies that will help compress your development timeline and maximize your return on investment.

Thermo Fisher has extensive experience with supply chain management, product manufacturing, and order fulfillment. We have a well-established manufacturing infrastructure to support IVD and MDx manufacturers around the world. We offer large-scale oligo manufacturing services as well as dedicated ordering and fulfillment services that can be integrated into your systems and processes. As a vertically integrated organization with ISO 13485:2016 certification, we can control reagent quality throughout nucleic acid synthesis. Our capabilities extend to the production of oligonucleotide components for IVD and analyte-specific reagents (ASRs).

We also offer a range of IVD instruments for real-time PCR and Sanger sequencing. Our general purpose **reagents for qPCR and sequencing** are suitable for use in MDx test development, and our existing IVDD-compliant assays and reagents can be used until their expiration dates. **New IVDR-compliant qPCR solutions** for enteric panels, virus detection, and sexual health evaluation are under development.

### IVD-compatible quantitative PCR (qPCR) instruments

Applied Biosystems™ QuantStudio™ Dx real-time PCR systems are part of a **comprehensive ecosystem** for IVD manufacturers and IHT developers. These real-time PCR systems provide flexibility for IVD development and investigational workflows. qPCR instruments that entered the EU market before May 26, 2022 can still be used after this date as long as they are supported by Thermo Fisher services and support. Products with the CE-IVD label will be compliant, even when the new regulation is fully applicable.

Each system has an IVD test mode that allows users to run only authorized IVD tests, which reduces the risk of unauthorized use or intentional misuse. IVD tests run on QuantStudio Dx real-time PCR systems have predefined run and analysis parameters to minimize run setup time, and each system can deliver results to a laboratory information system (LIMS) to reduce workload. The onboard software on QuantStudio Dx real-time PCR systems has security, auditing, and e-signature (SAE) features to help you satisfy IVDR requirements. The detailed experimental report includes a quality control (QC) summary, and information about reagents like lot numbers and expiration dates is stored and archived with each run.

### The QuantStudio 5 Dx Real-Time PCR System

The **Applied Biosystems™ QuantStudio™ 5 Dx Real-Time PCR System** is an accurate, sensitive, and reliable system designed for clinical laboratories. The QuantStudio 5 Dx system has CE-IVD certification under the IVDD and will be IVDR-compliant. The system enables laboratories to easily track samples associated with particular plates, sets of reagents, run dates and times, or data sets. The QuantStudio 5 Dx system is an interactive diagnostic instrument that enables short run times with minimal maintenance, and clinical laboratories can use existing plastic consumables for added convenience.

### The QuantStudio 7 Pro Dx Real-Time PCR System

The **Applied Biosystems™ QuantStudio™ 7 Pro Dx Real-Time PCR System*** combines modern hardware and software in a compact footprint, enabling IVD and MDx manufacturers to achieve maximum efficiency and greater accuracy in their workflows. Differences between target quantities as small as 1.5-fold can be detected in single-plex reactions, and the linear dynamic range of the system spans 10 orders of magnitude. The graphical user interface (GUI) supports end-to-end IVD workflows without requiring a separate computer, and centralized SAE settings can be applied to multiple instruments if they are networked. Maintenance and calibration records are automatically updated and can be printed on demand to document that the system has been maintained and calibrated to vendor specifications.

### TaqPath qPCR reagents

Applied Biosystems™ TaqPath™ qPCR master mixes are ready for MDx assay development and IVD applications. TaqPath master mixes are general purpose reagents labeled for laboratory use and are manufactured in an ISO 13485–certified and FDA-registered facility that adheres to cGMP principles. Our reagent manufacturing facilities provide the best quality management available with rigorous analytical and functional QC standards. Our superior QC standards and optimized TaqPath formulations help ensure excellent lot-to-lot consistency. We can also provide comprehensive documentation, including stability statements, supplier assessments, and change notifications, to simplify IVD assay submission and provide peace of mind.

### TaqMan custom primers and probes

The Applied Biosystems™ TaqMan™ portfolio of custom fluorophores and quenchers allows unprecedented flexibility for assay development along with the quality, consistent performance, and reliability of gold-standard TaqMan chemistry. Our probes provide outstanding signal-to-noise ratios and reproducibility, and they are manufactured in an ISO 13485–certified and FDA-registered facility with strict quality control standards. Documentation for our custom primers and probes is readily available to help assay developers comply with the IVDR.

### Sequencing solutions for molecular assays

We are proud to offer a suite of **genetic analysis instruments** designed specifically for regulated laboratory environments. The advanced thermal system of the **Applied Biosystems™ 3500 Dx Genetic Analyzer** for Sanger sequencing provides optimal temperature control for demanding DNA fragment analysis applications. It is the first capillary electrophoresis platform authorized for IVD use and is suitable for a wide range of applications, including microsatellite analysis, loss of heterozygosity (LOH) analysis, SNP confirmation and screening, *de novo* sequencing, and mutation profiling. It can also be used for sequence-based typing with Invitrogen™ SeCore™ HLA typing kits, and it is cleared for DNA fragment analysis with the Asuragen™ AmplideX™ Fragile X Dx and Carrier Screen Kit.

The intuitive user interface of the 3500 Dx Genetic Analyzer enables controlled and efficient run setup with preconfigured plate templates. Plate setup, data collection, and analysis are controlled through the onboard software, so hands-on time on the instrument is minimal. The system has SAE and radio frequency identification (RFID) features that enable you to track user activity and consumables, and built-in quality controls allow you to evaluate the quality of your data in real time. The 3500 Dx Genetic Analyzer includes a computer system and data collection software as well as an installation kit that contains your first set of accessories and reagents. Purchase includes full installation and operational qualification in addition to instrument training. The 3500 Dx Genetic Analyzer is backed by a comprehensive service and support plan with the option to purchase additional services depending on your laboratory maintenance and audit requirements.

The 3500 Dx Genetic Analyzer will be IVDR-compliant, and we are planning to stock our EU distribution center with IVDD-compliant instruments by May 26, 2022. This will help ensure continuous availability until the IVDR-compliant instrument is released. Fortunately, our IVDR-compliant instrument will have the same hardware as our IVDD-compliant instrument. Regardless of whether customers purchase an IVDD-compliant instrument now or an IVDR-compliant instrument later in the year, both platforms will be fully compliant throughout their life cycles.

We offer a full suite of reagents and consumables for the 3500 Dx Genetic Analyzer that currently have CE-IVD certification, including capillary arrays, polymers, standards, septa, and retainers. Our existing CE-IVD consumables will be upgraded to comply with the IVDR, and new IVD consumables will be manufactured to be IVDR-compliant.

## Services and support

### Instrument hardware qualification

Our instrument hardware qualification services can help you keep your instruments compliant. Our certified field service engineers are manufacturer-trained, and they can conduct and document comprehensive testing at your site. This includes determining your site requirements, software and hardware compatibility matrix testing, and component verification. We can also provide installation qualification (IQ), operational qualification (OQ), and instrument performance verification (IPV) or performance qualification (PQ) services to verify and document that your instrument meets performance specifications. Our IQ service provides documented evidence to verify that your instrument has been delivered and installed according to manufacturer specifications. Our OQ service provides documented verification that instrument subsystems are operating as intended and that the instrument meets the operational specifications of the manufacturer. Successful IPV and PQ confirm that your instrument can perform effectively and reproducibly, which can give you confidence in your results by verifying that the accuracy and precision of your instrument are being maintained.

## The AB Platinum instrument service plan

The AB Platinum instrument service plan is a top-tier, complete solution for maintaining optimal instrument performance and maximizing uptime. The AB Platinum plan is ideal for clinical and IVD laboratories that want the highest level of service and seamless support for timely delivery of results. The benefits of the AB Platinum instrument service plan include:

- **A 98% uptime guarantee.** Increase your testing confidence with a service plan that provides the comprehensive support your laboratory needs to deliver reliable results for patients.
- **Comprehensive repair coverage.** Repairs do not have to cause extended delays. Our unlimited comprehensive repair coverage allows you to keep your work moving.
- **Rapid response, on-site support.** Getting on-site support should not require long waits that leave you idle. A field service engineer will be at your location within one business day on request.**
- **Priority technical support.** Every minute counts when a problem threatens your productivity. The AB Platinum instrument service plan gives you 24/7 priority phone and email access to remote technical service and support specialists 365 days a year.† Our specialists can triage, troubleshoot, and resolve issues, including issues related to the digital and remote capability of connected instruments.
- **Planned maintenance.** Proactive instrument maintenance is the best way to help keep your system working optimally. Planned maintenance is included per instrument requirements.
- **Qualification services.** Documenting that your instruments are performing within manufacturing specifications is a vital step for your laboratory. The AB Platinum instrument service plan provides qualification services after planned maintenance visits and any major repairs.
- **Digital remote support.** Support technology should be as innovative as the systems it serves. The AB Platinum instrument service plan includes pioneering on-demand tools and capabilities like remote support with augmented reality technology, instrument-driven support, and instrument training.
- **Training.** A two-hour remote consultation with a field application specialist is included in the plan along with instrument training.

## The DataSafe Solution

Protect and rapidly retrieve your data with the flexible DataSafe™ Solution. The DataSafe Solution has end-to-end features that include consultation services, planning a data storage and backup strategy, system design, hardware integration, and ongoing support. The hardware component of the DataSafe Solution provides on-site storage with enterprise-class redundancy, which adds layers of protection for your data in the event of a disaster or hard drive failure. The DataSafe Solution can be scaled up if you require more data storage, so you never have to pay for more storage than you need.

If you would like to learn more about how we can assist you with your IVDR transition, read our Getting Ready for the IVDR blog.

* The QuantStudio 7 Pro Dx Real-Time PCR System is not available in all countries.

** Rapid-response, on-site support by the next business day is subject to regional availability.

† Priority technical support is available in the English language only.

Learn more at **thermofisher.com/IVDR**