Making sense of IVDR for LC-MS.

HOW TO INTERPRET AND PREPARE FOR THE NEW REGULATION (IVDR) ON LABORATORY-DEVELOPED TESTS IN MASS SPECTROMETRY (MS)

Making sense of IVDR for LC-MS.

Meet the authors

Magali Wolff
Head of Global Reagent Marketing and Support at Tecan

Magali Wolff has been with the company since 2001. Magali and her team of product managers are dedicated to providing Tecan's customers with the best service and quality products for their daily workflows.

Dr. Constanze Drechsel
Product Manager Autoimmunity and Infectious Disease Portfolio at Tecan

Dr. Constanze Drechsel joined Tecan in 2019. She has a scientific background and completed her PhD research in protein and allergy chemistry and now supports the Global Reagent Marketing and Support department with immunoassay and LC-MS solutions.

HOW TO INTERPRET AND PREPARE FOR THE NEW REGULATION (IVDR) ON LABORATORY-DEVELOPED TESTS IN MASS SPECTROMETRY (MS)

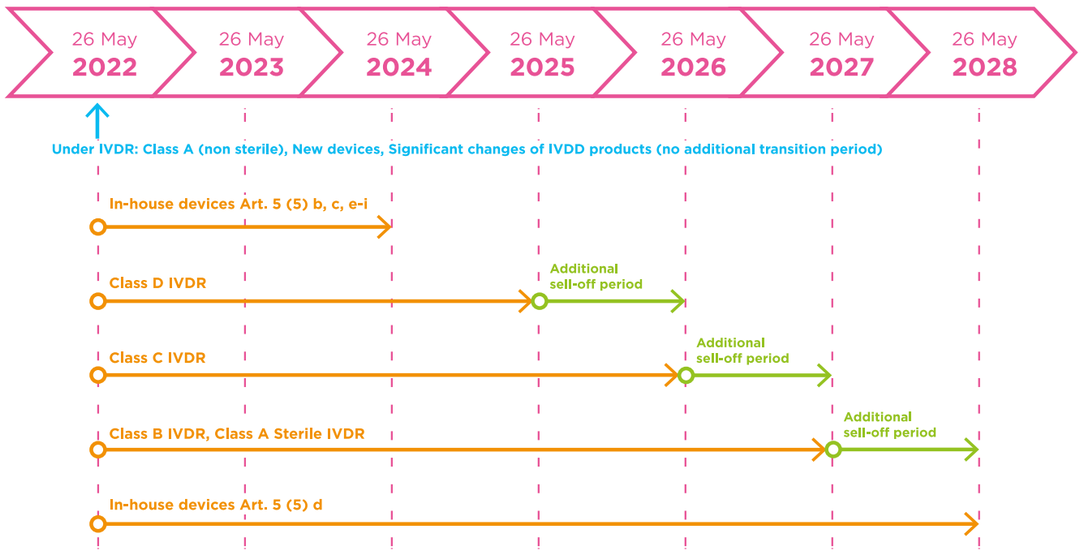
In Vitro Diagnostic Regulation (IVDR) is Europe's new set of rules designed to improve the quality, safety, and reliability of IVDs. Although IVDR is largely targeted at manufacturers, this new regulation also puts a higher burden on clinical labs, especially those doing Liquid chromatography–mass spectrometry (LC-MS), because they have implications for the use of laboratory developed tests (LDT, in-house devices or "home-brew" methods). Even if the tests are being run in non-EU labs, the IVDR may still apply if the samples being tested are from European citizens.

While we cannot ignore that new regulations like this can give rise to uncertainty as well as some additional work, we also see many opportunities for improving LC-MS workflows and diagnostic test performance. In this whitepaper, we aim to concisely dispel the uncertainty by breaking down important elements of IVDR to clarify where your laboratory stands. While changes are inevitable, we also aim to highlight opportunities that these changes can bring to your team and your lab.

IVDR Timeframe

The IVDR is already in place in the European Union. It entered into force in May 2017 and became applicable by law on 26 May 2022. In addition, there is a transition period giving device manufacturers and clinical laboratories the chance to make the necessary modifications in order to fully comply with IVDR by latest May 2028 (see Figure 1). Manufacturers of IVD devices have been working towards IVDR compliance for several years already. Many commercial devices for clinical mass spectrometry are already on the market, and companies and Notified Bodies are working closely together to achieve full compliance to IVDR by the end of the transition period. It is believed that the transition towards the IVDR will lead to some adjustments in the field of in vitro diagnostics, penalizing those manufacturers who did not do their homework. Tecan has partnered with the British Standards Institution (BSI) and already passed the audit of their quality management system according to IVDR criteria in early 2020 and now has products certified.

Despite the end of the transition period for the IVDR being postponed due to the COVID-19 pandemic, Tecan continues working on IVDR implementation. This approach is recommended to avoid any disruption of supply chains for routine clinical diagnostics.



Making sense of IVDR for LC-MS.

What is different about IVDR and how does it affect you?
The previous incarnation of the European regulations governing in vitro diagnostics was the In Vitro Diagnostic Directive (IVDD). There are a number of important changes and updates in the new IVDR that specifically affect LDTs. For the sake of the regulations, an LDT is a diagnostic test system that has been developed by the end-user laboratory to determine certain analytes in patient samples for clinical diagnostic purposes. In many cases, laboratories developed these methods to take advantage of in-house technical expertise or to decrease costs of consumables.

LDTs were specifically named and accepted under the IVDD (see IVDD Art. 1(5)). However, the situation is different under the IVDR. In mass spectrometry these kinds of clinical tests are widespread, be assured that you are not alone. In a survey performed by Tecan, 90% of participants stated that they employ LDTs in their routine workflows. Most of these professionals already feel a considerable burden of regulatory requirements.

Is there any way to avoid IVDR?
At this point, you may be wondering if it's possible to avoid IVDR altogether in order to continue using your lab-developed methods as before. Unfortunately, IVDR applies to all IVD devices on the European market and this includes assays based on LC-MS. The regulation also applies to products and processes that have existed for decades, meaning that there will be no 'grandfathering' under the IVDR.

Clinical laboratories producing LDTs are considered to be manufacturers which requires a significant adaptation of the quality management systems of these institutions.

Is IVDR the end of LDTs?
A major criticism of IVDR has been the potential threat it poses to the use of LDTs. Reducing the vast pool of hard-to-regulate tests in favor of a few commercially available solutions may seem like a good idea from a patient safety standpoint, however there are also some drawbacks. Firstly, experts worry that the lack of diversity of tests caused by the high regulatory burden will mean that for some patients, the right test is simply not available. Critics also worry that IVDR will result in a lack of innovation in the diagnostic test space meaning that new and improved solutions will be developed less often.

With this in mind, it is important to know that laboratory-developed tests are not prohibited by the IVDR. In fact, in contrast to earlier directives, the IVDR clearly maps the future of laboratory developed tests (e.g., mass spectrometric assays) after the transition period that for LDTs ends partially in May 2024 and completely in May 2028. These are the four most important take-aways from the IVDR for clinical laboratories, which are listed in article 5(5):

1.) **LDTs can only be used, if there is no equivalent device on the market that fulfils the needs of the respective patient group. A justification of non-equivalence based on technical, biological or clinical aspects of the device must be documented (later also updated, should equivalent CE-Marked IVDs become available in the market).**

IVDR ARTICLE 5(5) (d)
"the health institution[1] 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."

2.) **A suitable quality management system must be in place. 'Appropriate' means that it should be compliant to ISO 13485 or ISO 15189.**

IVDR ARTICLE 5(5) (b)
"manufacture and use[2] of the devices occur under appropriate quality management systems;"

IVDR ARTICLE 5(5) (c)
"the laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation"

3.) **For every laboratory-developed test, laboratories need to install a surveillance and traceability framework and investigate the performance of the device even after the initial validation of the device.**

IVDR ARTICLE 5(5) (i)
"the health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions."

Making sense of IVDR for LC-MS.

4.) Although laboratories must not fulfil every aspect of the IVDR, they are required to comply to Annex I of the IVDR. Annex I holds the general safety and performance requirements of the IVDR and represents the lion's share of the regulatory requirements for these devices under the IVDR.

IVDR ARTICLE 5(5)

"With the exception of the relevant general safety and performance requirements set out in Annex I, the requirements of this regulation shall not apply to devices manufactured and used only within health institutions established in the union."

Furthermore, the IVDR narrows the use of laboratory-developed tests to single entities within a parent organization, so you cannot provide MS based test results to another laboratory. IVDR requires that you provide information about the risk classes of devices, and requires publicly available information about conformity to the regulations. A declaration must be drawn up and published (e.g. via the health institution's web site, confirming compliance with the general safety and performance requirements of Annex I, Article 5(5) (e).

It is recommended to perform a self-assessment for any LDTs. Legislators have forged the IVDR to toughen the requirements to improve the performance as well as the post-market surveillance of diagnostic devices. Consequently, the regulation also covers testing methods that are not provided by dedicated manufacturers of IVD devices but have been developed by specialists in routine clinical diagnostics - so-called in-house devices.

Clause 29 of IVDR:

"Health institutions should have the possibility of manufacturing, modifying and using devices in-house and thereby addressing, on a non-industrial scale, the specific needs of target patient groups which cannot be met at the appropriate level of performance by an equivalent device available on the market. In that context, it is appropriate to provide that certain rules of this regulation, as regards devices manufactured and used only within health institutions, including hospitals as well as institutions, such as laboratories and public health institutes that support the healthcare system and/or address patient needs, but which do not treat or care for patients directly, should not apply, since the aims of this regulation would still be met in a proportionate manner. It should be noted that the concept of 'health institution' does not cover establishments primarily claiming to pursue health interests or healthy lifestyles, such as gyms, spas, wellness and fitness centers. As a result, the exemption applicable to health institutions does not apply to such establishments."

So while the use of in-house methods is not at all prohibited, it has clearly become a lot tougher to meet the regulatory requirements. This means that if there is an off-the-shelf solution it would be better to use this in every instance where it is appropriate and produces acceptable results. Off-the-shelf products are often very good if they are properly evaluated and validated. In the time leading up to May 2024, it may be valuable to begin evaluating and validating commercial offerings to see if they can replace any of your in-house options. It is also worth opening a dialogue with manufacturers to understand how they are addressing the regulations, and whether they have products in the pipeline that could be used in your lab. At this point, if there are any tests that are done in your lab that cannot be sourced from an accredited commercial supplier, you can focus on meeting the regulatory requirements for only those few, 'select' tests.

Next steps for your lab.

WHILE THE TASK AHEAD MAY SEEM DAUNTING, THERE ARE SEVERAL CONCRETE STEPS THAT YOU CAN TAKE NOW IN ORDER TO STREAMLINE YOUR TRANSITION INTO IVDR.

Identify commercial alternatives
Map out your existing LDTs and start compiling a gap assessment to address the following questions:

- Do any of your LDTs fall under the IVDR in-house exemption?
- For which of your laboratory-developed assays are there no alternatives available?
- Are there any CE-marked commercial kits available that could be used as alternatives for any of your LDTs impacted by IVDR?

Following this, compile an overview of the clinical performance data that is available for all your methods. Good and accurate documentation, whether gathered in-house or provided by a commercial supplier, will help you to understand whether your tests comply or not. Once you have a clear understanding about the gaps with respect to what the IVDR allows, you will be able to allocate your resources wisely. This could be a really useful exercise in pinpointing areas where time and money can be saved in your typical workflows.

Check your laboratory-developed test against the guidelines
For the laboratory-developed tests that are unavailable from any other source, perform a gap analysis against the General Safety and Performance Requirements (GSPR) checklist. Below are the most critical sections against which to validate your in-house tests. In addition, further details on the required documentation are provided in MDCG 2023-1.

Firstly, does your test live up to the performance requirements and can you prove it with data?

IVDR Annex I.1
"Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art."

Then ask if you have a Risk-Management-Plan that addresses process and product-related risks. (What are the risks that affect the safety of your device. How do you mitigate them?)

IVDR Annex I.4.(1)
"Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To reduce risks, the manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable."

Finally, can you provide a Post-Market Surveillance Plan (How will you proactively collect and review the experience gained from your device after introducing it to routine use? How will you apply necessary corrective or preventive actions?)

IVDR Annex I.09.2
"The performance characteristics of the device shall be maintained during the lifetime of the device as indicated by the manufacturer."

The full list of general requirements for safety and performance can be found in Annex I of the IVDR.

Calculate your return-on-investment
Whether choosing a new commercial supplier of tests or staying with your laboratory-developed solutions, there will be a financial and time commitment for whichever decision you take. When implementing new methods or adhering to new rules, it is essential to evaluate the IVDR-readiness of new procedures. Consider your return-on-investment of laboratory-developed mass spec assays up until May 2024. It is possible that it is not financially feasible to invest time and resources into the validation of a method that is difficult to maintain after the end of the IVDR transition period. For example, it could take one full-time employee several weeks to implement and validate a new chromatographic method including tuning of analytes on the mass spec. In this case, the financial break-even-point for this method may lie beyond the deadline for IVDR. Therefore, this implementation may not be profitable even if it is legally possible to run this assay inside a clinical diagnostic laboratory until the end of the transition period. It is essential that you know your numbers and that you let them help guide you to make the right decision for your lab.

This is, of course, not to say that commercially available options are not without cost; however, the costs associated with commercial solutions are typically more transparent as they come with prices and quality assurance documentation.

It is essential to look deeply into your lab process and truly uncover your options to navigate through the changing regulatory environment. Tecan can help you develop solutions that are compliant with IVDR, so that you can focus on your patients instead of on paperwork.

Conclusion
The IVDR deadlines are coming and there is plenty of work to be done, but the path ahead has become clear. You now have time to audit and evaluate your methods and adapt them if needed. Although the new IVDR represents a regulatory burden, you don't need to carry it yourself. Commercial partners like Tecan are well prepared to help you navigate the IVDR landscape, including taking on much of the paperwork, tracking and regulatory issues. Many labs would rather put the regulatory burden in the hands of a third party but are rightfully concerned about commercial tests not being fit for their needs. If that is the case for you, then now is the time to reach out to commercial partners. Now that commercial diagnostic manufacturers have a handle on the regulations, they can develop kits and assays of interest for the coming years. Now is the time to start a dialogue with them to see if they can support you. Validation of new commercial kits can take time, but it doesn't have to be an arduous process and may very well save you money in the long term.

REFERENCES:

1 See MDCG Guidance (2023-1), section 2.

2 For more information on the manufacture and use of devices see MDCG Guidance (2023-1), section 3.2.2.

Tecan sales organizations

Australia +61 3 9647 4100 **Austria** +43 62 46 89 330 **Belgium** +32 15 42 13 19 **China** +86 21 220 63 206 **France** +33 4 72 76 04 80 **Germany** +49 79 51 94 170
Italy +39 02 92 44 790 **Japan** +81 44 556 73 11 **Netherlands** +31 18 34 48 17 4 **Nordic** +46 8 750 39 40 **Singapore** +65 644 41 886 **Spain** +34 93 595 25 31
Switzerland +41 44 922 89 22 **UK** +44 118 9300 300 **USA** +1 919 361 5200 **Other countries** +41 44 922 81 11

Tecan – Who we are

Tecan (www.tecan.com) helps to improve people's lives and health by empowering customers to scale healthcare innovation globally from life science to the clinic. Tecan is a pioneer and global leader in laboratory automation. As an original equipment manufacturer (OEM), Tecan is also a leader in developing and manufacturing OEM instruments, components and medical devices that are then distributed by partner companies.

Founded in Switzerland in 1980, the company has more than 3,000 employees, with manufacturing, research and development sites in Europe, North America and Asia, and maintains a sales and service network in over 70 countries. In 2021, Tecan generated sales of CHF 947 million (USD 1,041 million; EUR 877 million). Registered shares of Tecan Group are traded on the SIX Swiss Exchange (TECN; ISIN CH0012100191).

402477, V 1.0 2022-12

www.tecan.com

TECAN.