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What You Need to Know About Clinical Evidence For The EU IVDR

by Amanda Maxwell

With growing urgency for the IVD industry to start compliance with the IVD Regulation, NSF's Robyn Meurant explains the importance of getting clinical evidence right first time

The EU's IVD Regulation is going to really shake up the IVD sector because it raises the regulatory bar so much higher for the vast majority of products entering the market.

For the IVDR, nearly all IVD manufacturers need to engage the services of a notified body, and in so doing, demonstrate for the first time that their products have sufficient clinical evidence to meet regulatory requirements. Moreover, clinical evidence demands are much higher than under the current IVD Directive.

The challenge facing most manufacturers is if they can successfully do this by 26 May 2022, the date of application of the new regulation.

Robyn Meurant, executive director, regulatory services, IVDs and medical devices, at NSF Health Sciences consultancy, explained more in a recent interview with *Medtech Insight*:

Q **Medtech Insight: Given that most IVD companies will have to demonstrate for the first time that their products meet clinical evidence requirements under the IVDR, what impact is this likely to have on resources and timelines?**

A Robyn Meurant: Many companies have IVDs with varying levels of evidence (quantity and quality) as was required to meet the IVD Directive. The requirements for clinical evidence for the new regulation are both comprehensive and prescriptive, with an emphasis not just on demonstrating analytical performance, but also how the IVD

offers clinical benefit and how it can be considered state of the art.

Re-evaluation of existing evidence is a first step, followed by a gap analysis and then generation of new clinical evidence to ensure the device conforms. Fortunately, the requirements of the IVDR for clinical evidence have flexibility and permit, with justification, the use of real world data as well as evidence obtained from peer-reviewed literature.

This means new literature searches are needed, not only for clinical performance evidence but also to demonstrate scientific validity and state-of-the-art. In addition, a comprehensive performance evaluation report will be required. A post-market performance plan needs to be put in place that proactively collects performance data to show ongoing conformity or to ensure missing clinical data is generated. These are just some of the new activities that need to be implemented under the IVDR. Depending on the range of products, their claims and in part, their risk class, this represents a lot of work and, obviously, resources.

Q **How will companies manage the increased burden of evidence?**

A Meurant: The large manufacturers I work with are investing heavily to meet the regulations, but I worry for SMEs with a broad range of critical IVDs. My other concern is that we still know of firms that have not even started the process. They truly have underestimated the effort to cross the line on 26 May 2022.

Q **Under the IVDD, which products have needed to demonstrate clinical evidence and what lessons can we learn from how that has been managed, and in terms of how much additional work will be ahead for IVD companies under the IVDR?**

A Meurant: Clinical evidence is required for nearly all IVDs. A common misunderstanding is that lower risk products, that have been non-list A/B under the IVDD, will not need much work to meet requirements.

The level/amount of clinical evidence that will need to be generated can certainly be influenced by the risk class, but this is only one factor that must be taken into consideration.

Even if you have a product in the highest risk class (List A, Annex II) according to the IVDD, there are still many new requirements under the IVDR, and we need to remember that we have not yet seen the common specifications for these products, the new testing requirements that replace those of the IVDD. This will require additional work focused on the two questions around 1) what are the new requirements that impact my technical file? and 2) the gap analysis with what I already have?

Q **Notified bodies and their staff historically do not have a great deal of experience evaluating how clinical evidence requirements for IVDs have been met. Do you feel confident that there are going to be sufficient notified body IVD resources to ensure that clinical evidence can be reviewed in time so that the IVDs can be compliant by 26 May 2022?**

A Meurant: I think that the notified body situation for IVDs is dire. However, if you have already engaged a notified body for your IVDs, it is important to realise that the staff reviewing your technical files are indeed subject matter experts.

The new notified body designation process insists on this. Don't gamble on under-capacity of notified bodies giving cursory glances to technical files. It won't happen.

Q **Which IVD product categories are likely to have the biggest challenges in complying with clinical evidence requirements and why?**

A Meurant: Companion diagnostics are a difficult area, given the lack of guidance on the expectations for meeting both notified body and European Medicines Agency (EMA) requirements.

Legacy products that have been on the market with outdated technical files are also

an enormous issue. They are a bit of a minefield, Not only is some data old, but a revised performance evaluation may indicate that the device is no longer be considered state of the art.

Legacy products may have performance claims that have increased with time without sufficient evidence to support them. In addition, this old data may have been generated using a comparison with a predicate device (meeting FDA 510(k) needs). This approach (demonstration of equivalence) is rarely supported by the IVDR and will prove even more difficult if the predicate device has not been CE marked according to the new requirements. In my opinion, it will only be newer generation products with minimal changes that can use an equivalence route to leverage performance compared to an equivalent device.

Q What factors determine how much clinical evidence is needed?

A Meurant: We always start with the intended use statement, and that usually takes us firstly to the risk classification. This is a good starting point, but it goes hand in hand with other issues such as novelty (technology or biomarker), all claims and users.

In addition, a new biomarker may need not only performance data, but extra data generated to support scientific validity. Self-tests and near-patient tests require specific evidence generated by users' representative of those whom are expected to use the test, not the company R&D team.

Q What is the importance of EU IVD standards in terms of clinical evidence and do you think they will be ready in time? If not, what should companies and notified bodies do?

A Meurant: EU standards are without doubt important for many aspects of design, development, quality systems, labelling etc.

At this point of time, no standards have been harmonized to the IVDR. But that must not be an excuse to stop using IVDD harmonized standards, or new versions of IVD

standards.

Remember, the latest version of standards, by their inherent nature, are considered state-of-the-art. In my experience, when it comes to IVDs, we need to look not only at latest versions of standards products by the International Standards Organization (ISO), but importantly, also at the standards produced by the Clinical & Laboratory Standards Institute (CLSI), the World Health Organization (WHO) and other standard setters. When guidance that is not harmonized is used, don't forget to provide a rationale as to why you consider this to be best practice.

In the absence of relevant guidance here, I would even suggest that for newer technologies, guidance produced by the FDA can help in providing a valid approach to study design and fulfilment of safety requirements. Whatever you use for your clinical evidence, remember, it should be well justified in your documentation.

Q **Where do Common Specifications (CS) fit with clinical evidence?**

A Meurant: The CS provide a clear direction for minimally meeting clinical evidence for many general safety and performance requirements (GSPRs), if they cover the intended use of your device. Any extra claims will still need further clinical evidence. The CS, though, do not obviate the need for generating and/or reporting scientific validity evidence.

Q **What about clinical evidence for companion diagnostics?**

A Meurant: The crunch is that a manufacturer must have evidence of the suitability of their IVD in relation to the medical product concerned. It is generally acknowledged that co-development of the IVD and the drug is the best way to gather this evidence if possible. This is about the sum total of what we know.

There is a real need for more guidance to ensure the IVD company knows not only what evidence will meet the notified body's assessment but also what will satisfy the medicine's regulator (probably the EMA).

Q **There are 19 months now until the IVDR full application date. What would you be advising IVD manufacturers to be doing now to ensure that they meet the deadlines in terms of clinical evidence?**

A Meurant: First and foremost, ensure you have engaged the services of a notified body which has the designation scope covering your device. Communicate with them as much as possible to ensure you understand their expectations. I also recommend ensuring your company (and not just the regulatory affairs staff) has a solid understanding of the expectations of the new regulations.

You will need them all to understand your timelines and budget for accumulation of satisfactory levels of clinical evidence.

Finally, given notified body time will be precious, seek an external review of a technical file and your clinical evidence. No one can afford long assessment times.

If you have non-conformities identified by the notified body in your clinical evidence, do not think they can prioritize multiple reviews of your attempts to rectify them. "Get it right first time" is the message.

Q **How important is continuous performance evaluation and how should manufacturers prepare to meet the IVDR requirements for this?**

A Meurant: The IVDR is written with the aim of only having conforming devices on the market. The way this is to be accomplished is through additional, reiterative post-market activities. A manufacturer must have systems in place to ensure performance evaluation post-market is a process involving an evidence and risk-based plan that ensures effective monitoring, review and re-evaluation of clinical evidence.

Ensure your post-market plans are optimized to your devices, and that they include proactive measures. This is an aspect the notified bodies will be paying close attention to.