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# Regulatory Fragmentation in Europe and Its Risks for Patient Access and Safety: Subcontracting Work Flow Steps of In-House Diagnostic Procedures

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**Guest:** Dr. Raymond Nistor is a neurosurgeon and medical device safety expert, and head clinician at QMD Services in Vienna, Austria.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. In Europe, as in the United States, care for patients with rare diseases often requires testing that's not available from commercial in vitro diagnostic device manufacturers. In these cases, hospital laboratories rigorously validate their own test methods, termed in-house in vitro diagnostic devices in Europe and laboratory-developed tests in the United States. The European Union's In Vitro Diagnostic Regulation, or IVDR, forces laboratories offering IH-IVDs to abide by strict requirements, but does not clearly state whether any of the steps may be subcontracted to a third party with greater resources or subject matter expertise.

Further, different countries' regulatory bodies interpret this regulation differently, which means patients in one country may have access to testing, while those in another will not. Clearly, the regulation's original design was not to slow innovation or limit access to medically necessary testing, but that appears to have been the unintended consequence. Where does Europe go from here? And can the US District Court's ruling vacating the FDA's final rule on LDTs serve as a roadmap? A new special report, appearing in the December 2025 issue of *Clinical Chemistry*, focuses on the European Union's IVDR, describes its impact on test availability in member countries, and proposes solutions to eliminate regulatory heterogeneity, while reducing unnecessary burdens on clinical laboratories.

In this podcast, we are pleased to welcome the article's lead author. Dr. Raymond Nistor is a neurosurgeon and medical device safety expert with over 40 years of clinical, industry, and regulatory experience. Formerly Corporate Medical Device Safety Officer at Baxter and now Head Clinician at QMD Services in Vienna, Austria, he works to rebalance EU device regulations, fostering patient safety, innovation, and practical compliance for in-house diagnostics. So, Dr. Nistor, your article says the In Vitro Diagnostic Regulation, or IVDR, was meant to harmonize safety and quality across Europe, but has instead created confusion and regulatory fragmentation. So, what went wrong?

Raymond Nistor: Well, I think the In Vitro Diagnostic Regulation for the listeners outside of Europe, it's important to mention, this is a regulation which was published in 2017, got effective 2022, so we had also a transition period to this new regulation, and it was genuinely written for manufacturers. What does that mean? Because it was the first time when a regulation written for manufacture was touching also this area of in-house diagnostics for clinical labs, and this was totally new.

We have clinicians, and my co-authors, we are in full agreement with the regulation with its goal to allow every patient to be exposed only to clinical tests, which regardless, whether they come from a manufacturer or they come from a laboratory as so-called in-house tests, also known for our US listener, these are the laboratory-developed tests. In fact, it's just a verbal difference here. Regardless where they're coming from, they should meet the same standards of quality, of diagnostic precision, of patient safety. Basically, that is a good intention, but it was written in a way that it left a lot of open space for interpretation.

So, let me go into that specific article, and mind you, there are 113 articles, which define what manufacturers should do in terms of design, in terms of developing, in terms of bringing these products to the markets in the European Union. One of these articles, namely Article 5(5), defines what we call here in Europe, the Health Institution Privilege. The Health Institution Privilege refers to labs, who are developing, manufacturing, and using in-house diagnostic tests, and they are exempted from the regulation if they prove that their in-house tests comply with the core of the law, which is Annex 1. And Annex 1, for the non-regulatory people amongst us, the Annex 1 is basically the minimal requirements for manufacturers to bring their product to a certification to get the CE mark and to place the products on the markets in Europe.

They are called GSPR, the General Safety and Performance Requirements, which set the bar so to say for a diagnostic test, but for manufacturers. What went wrong is that the regulator has overstepped here, similar to the FDA with the Final Rule on LDTs, they overstepped a little bit their authority and their competence, although they were very concerned about safety, which again we are supporting also for in-house tests. It ignored totally the clinical laboratory reality. Each national authority, because we have Ministry of Health in most of the countries, we have 27 member states in the European Union since the Brexit, and each national authority, which is supposed to enforce this Article 5(5) with the laboratories had a different interpretation. So, basically, we ended up in 27 interpretations of one good intention. Basically, this fractured Europe. In practice, we had a very good intention, which in practice, turned out to be what we

call regulatory fragmentation, different interpretation of the law.

Bob Barrett: Well, you stressed several times that the IVDR was drafted for manufacturers and not for laboratories. Why does that distinction matter so much?

Raymond Nistor: Well, it matters because as I previously said, the regulation was based on a manufacturing logic, on the technologies, on the steps, how a manufacturer develops, manufactures, and places the product on the market, on the European market. As soon as that product receives the CE mark and is placed on the market, it's literally out of control of the manufacturers. You cannot control -- think about the pandemic. You have a manufacturer, they come out with a corona test and they do these tests, but there is no control of the manufacturer. It depends on the user. It depends on the patient. It depends on so many factors. So, it is legitimate for the regulator to say, hey, we have to do a pre-market certification, as also the FDA does, and we do a post-market surveillance of the markets. But that discovers only the top of the iceberg, because it is a mechanism which cannot control the entirety of the market.

With laboratories, which develop their own tests and use them on their own patients, it is a totally different situation because you use the test in your controlled environment, and mind you, laboratories have their quality controls. They have their systems to supervise, and quality checks, which are done by clinical professionals. The product which is used there in those laboratories is addressing a very highly selected population of patients, namely the patients which are the patients of that health institution. So, we compare here the entirety of a hard to control commercial market with the controlled environment of a clinical laboratory.

So, applying the industrial framework to the settings of a laboratory, that's where the difference is. That's where it went wrong. So, instead of having a clinical process, you now push the laboratories to do a lot of paperwork to address things which they are not qualified, because they don't have regulatory experts and quality management experts, but manufacturer have. Again, we share the vision of the regulation that patient safety and precision of the testing and performance of the testing should be the same for these two categories, but the clinical reality was ignored in our opinion.

Bob Barrett: Modern diagnostics relies on sequencing, bioinformatics, and now AI. Can laboratories outsource some of those steps under the IVDR, and if so, how can they do that?

Raymond Nistor: Yes, they can, and for that, we need to keep in mind, today, clinical laboratory diagnostics is not anymore one tube in one

room. It is, they are complex tests, they are niche tests, as you said, deep sequencing, bioinformatics, and even AI in the meantime, with image analysis and pathology. The regulator in Article 5(5) is saying that you should use this privilege for your in-house devices, but you're not allowed to transfer this device from your health institution into other health institution. That is forbidden.

In our interaction and research with regulatory experts, with laboratory experts, we very often became the question well, but sometimes I cannot afford experts in oncology and I need to partner with other labs, with other manufacturers, or even with digital service providers. For that, I need to subcontract their services, to outsource. It's probably better to talk about partners, because again, it's the partner of that hospital. It's not that rigid supply of chain control which you have with manufacturers. Ultimately, you can do it, that's a short answer, but to do it, you have to satisfy some important conditions, and there are three. Namely, first of all, the responsibility stays in the originating laboratory, in the laboratory which used the test on the patient and delivers the results for the clinical decision process.

So, ideally, that original lab should be ISO-15189 accredited, which is the international standard for medical laboratories to ensure the traceability and the oversight. Secondly, the partner, the subcontractor, must also be certified to have a quality management system in place to trace what they are doing. So, if that partner is another laboratory, it's the ISO-15189, the laboratory standard. If that partner is industrial, then you have the ISO-13485, and if that partner is a digital service provider, you have the standard for information security, cyber security, and privacy protection, the 27001. But literally, these two partners; then, number three, they have to create a risk-based quality assurance agreement, and the originating laboratory has to continuously monitor the performance of his subcontractor, because they are critical supplier.

This is pretty much the same as sterilizing a single-use instrument. You have a sterilizer, I'm the manufacturer. I sent my devices before I put them on the market to a certified sterilizer but I'm responsible for the stability of that device or what we are producing. And those outputs of your partner need to be validated. So, the framework keeps the clinical responsibility in the originating institution but enables collaboration because this type of collaboration is easy to handle in highly sophisticated laboratories and academic laboratories, but it's hard to handle in small little hospitals or small labs, which do not have the resources to control their supplies.

Bob Barrett: In your paper, it highlights the growing use of "Research Use Only" products. Why are manufacturers doing this and what does it mean for laboratories and patients?

Raymond Nistor: This is a byproduct of the IVDR complexity. For many niche products or low volume tests, the costs and the workload for recertifying products over waste their commercial value. So, manufacturer withdrawal legacy CE mark devices under the old directive, which was not the regulation, and they withdraw these assets from the market and re-label them research use only products. What does that mean? Well, number one, research use only products are not in scope of the In Vitro Diagnostic Regulation. Secondly, you don't have to produce them under scrutinized quality control management systems, as you would do that with a commercial product. So, basically, it's not illegal to use those products if you do some research. It's a problem, because the responsibility now shifts from the manufacturer which says, this is for research, you don't have to worry. You're not allowed basically to include this kind of research use only product in your clinical decision-making process for patients. So, it's just for research, as the name says.

What happens now, the tests are available. Labs are acquiring these tests and including them in their clinical workflows, and they have now to validate these tests and to make them compliant with the requirements of Article 5(5), because that is an in-house test. It's not a commercial product anymore.

So, large centers can do that and can manage that but small hospitals struggle with documentation load. The risk is not lower; it just shifts from the manufacturer to the lab, and by that, it captures a lot of the capacity, the resources of labs, and by that they slow access for patients ultimately. In 2024, we received a new ISO standard, ISO 5649, which is the standard for manufacturing, designing, and validating in-house tests or laboratory-developed tests. It's an international standard, which gives laboratory a structure and from the standpoint of the regulation, defensible way to show this responsibility in the transparent and regulatory compliant way.

Bob Barrett: Well, finally, Dr. Nistor, what should you have learned from the US court decision that overturned the FDA's rule on laboratory-developed tests, and looking ahead, what's the way forward for the IVDR.

Raymond Nistor: So, first of all, I must say the motivation of writing this publication was not to complain what went wrong and complain as many do about this regulation, and we have seen that a US court has confirmed that the quality oversight belongs into the CLIA and not into the FDA. This is not going to happen in Europe. We have a different jurisdiction. We

don't have a federal code of regulation, so a court cannot invalidate the regulation of the European Union. But Europe faces exactly the same challenge. The regulator overstepped somehow its capabilities and entered an area which shouldn't be under this control and as to European Federation of Clinical Chemistry and Laboratory Medicine, the EFLM, the Biomed Alliance in Europe, and mainly professional association have repeatedly conveyed to the European commission, we need to respect this principle of subsidiarity and trust accredited laboratories.

But there is a but here, and that is accreditation in Europe is not compulsory in all the member states. France and Hungary have a compulsory accreditation under ISO-15189, the laboratory quality and performance standard, but it's not compulsory in the rest of the countries, or just limited to high-risk specialties in the diagnostic world. So, the regulation should rely on two pillars. One is a clear clinical justification for each in-house test and a documented quality management system under ISO-15189. Secondly, the new standard for laboratory developed tests, the ISO 5649, provides basically a bridge, and we have demonstrated this in one of our tables in the publication, where we compared the requirements of the law with the chapters of this standard.

Basically, if you follow the standard, which is very practice driven, you basically are compliant with the regulation. So, if we adopt this approach, and this is a solution, this is not written anywhere and we did our research and our homework. We keep the regulator's intention of equal quality with clinicians' mission alliant, and that's good about it, because we should not expect that those regulators, who with good intention have over-regulated laboratories, will fix this soon. Right now, the European Commission is undergoing a public consultation to improve and simplify the regulation. But from our discussions with experts, we know that Article 5(5) is very low on their priority list, but I'm optimistic with such approaches and with input from the professional societies, we will come to a change from the diagnostic community. We will have this driven by the diagnostic community, which understands the lab reality.

Bob Barrett: That was Dr. Raymond Nistor from QMD Services in Vienna, Austria. He wrote a special report in the December 2025 issue of *Clinical Chemistry*, advocating for regulatory changes in Europe to ensure access to safe, accurate, in-house in vitro diagnostic testing, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thank for listening.