Johner Institute

New requirements under the IVDR for laboratory-developed tests (LDTs)

With Dr. Sebastian Grömminger, Prof. Dr. Christian Johner

Transcript

00:00:05 Speaker 1

Medical Device Insights, a podcast by the Johner Institute for medical device manufacturers, authorities and notified bodies.

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The M.D.R.

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will be postponed by one year, the I.V.D.

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Probably not.

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And so many do not have exactly what to expect on their radar.

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and in contrast to the M.

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D.

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R.

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even more products will be subject to the new regulation.

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And what these requirements are, which products will be newly affected, we are discussing today with my colleague, Doctor Sebastian Gremmegger.

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Hello, Sebastian.

00:00:46 Speaker 2

Hello Christian, hello.

00:00:47 Speaker 1

So that our listeners know who you are, it would be possible for you to introduce yourself very briefly.

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Yes, very much.

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I am Sebastian Gröminger, as you have already said, and I am the head of the I.V.D.

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Group or the I.V.D.

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Teams at the Jona Institute.

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And we have the responsibility to advise our customers at the Jona Institute, holistically for the approval and marketing of in vitro diagnostics, regardless of whether it is an essay or an I.V.D.

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Analyzer.

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Or even an I.V.D.

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Software or, as in today's topic, the Laboratory Develop Tests.

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Ah exactly, because that's what it's all about, the L.D.T.s and maybe let's first take a look at who this is a change for.

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So those who are particularly interested in the I.V.D.

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is affected.

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In particular, the new I.V.D.

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Regulation or we abbreviate it today to I.V.D.R., are of course primarily the manufacturers of in-vitro dia-

gnostics, from the C.E.

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marked or

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or rather, C.E.I.V.D.

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products, the manufacturers are affected.

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Then, of course, we also have the distributors and all other economic actors, as we do from the M.D.R.

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But here something completely new comes into play, namely that this time the I.V.D.R.

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with its introduction also takes the laboratories into account, and this has the background,

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that of course the laboratories also offer in their services what is associated with C.

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E.

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is used when we use our own developments in the laboratory and make them available to the patients or the treating physicians.

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Do I understand you correctly?

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So, we have something similar here, which the M.

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D.

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with the concept of self-production.

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Only in this case it is now

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not the hospitals that do the in-house production, but the laboratories.

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Exactly, in principle you can look at that equivalently.

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What rules do these laboratories all have to comply with now?

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So you've already mentioned 1, that's the I.

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V.

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D.

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R.

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Are there any other regulations we should be aware of?

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Yes, so far there are also the regulations in the

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by the German legislator.

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On the one hand, there is the Medical Devices Act, the Medical Devices Operator Ordinance and the Medical Devices Safety Plan Ordinance, as well as the Medical Devices Ordinance, which also includes the performance evaluation, i.e. the clinical studies that must be carried out so that we can place products on the market in a compliant manner.

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In principle, this has so far been regulated by the German legislator for medical laboratories and then it will at least

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on a general level to the European level in the I.

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V.

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D.

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R.

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upscale.

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Now you just said that some laboratories will be affected by these changed regulations.

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Does it now affect all laboratories or is there, for example, if a laboratory is now more research-oriented, they must also take it into account.

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No, so purely research-based laboratories are exempt from this, these are laboratories that use research use products,

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i.e. for Research Use Only Claims are attached to the products and they also use devices for general laboratory purposes.

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They are not affected here.

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So when it comes to purely academic research, it can be absolutely ruled out.

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But there are laboratories that are of course at the limit there, for example new C.

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E.

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marked or to C.

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E.

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Test the marking of pending products.

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So also the consultant laboratories, such as

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Now the frequently quoted Drosten Laboratory in Berlin also uses products that don't require a C.I.

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should be marked.

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They are, so to speak, in an intermediate stage for products for performance evaluation purposes.

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Only then are the laboratories really affected, which actually then carry out the determination of results for patients in the sense of a medical laboratory.

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O.

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K., that means we now have several cases that we have to keep apart.

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We have these research only things that don't fall down.

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Then we have

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Laboratories that try out products in a certain way, yes, there are those who are active in performance evaluation and then we have laboratories that really use their own products to serve the diagnosis of patients and it is precisely for this last group or this last group that it is about, it is now about here and the regulations are now explicitly addressed to them.

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That's exactly how you can understand it

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And then we may have to distinguish the case that there are laboratories that exclusively use C.E.I.V.D.

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use marked products, according to the instructions for use that the manufacturer provides and those that fine-tune it or maybe even a ‚let's maybe develop a competitor's product for it and then use it' or maybe one that

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fulfils a further purpose or a supplementary purpose, perhaps by addressing a group of patients who are affected by the C.

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E.

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I.

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V.

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D.

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is not taken into account on the market.

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O.

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K., but it was important that you pointed it out because C.

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E.

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All products or a lot of them probably have markings now, but we're talking about C now.

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E.

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I.

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V.

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D., i.e. declaration of conformity with regard to I.

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V.

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D.

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D.

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or the I.

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V.

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D.

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R.

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Exactly, what were the reasons

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for the fact that I.

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R., which we are talking about right now, has decided to regulate this issue of self-production.

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Yes, in principle, the legislator, the European legislator, has recognised here that if you look at the topic of in vitro diagnostic medical devices holistically,

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that laboratories must not be left out for the reasons mentioned.

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If we imagine the scenario, it doesn't matter whether the patient comes to the doctor, gets treatment and then gets the doctor's advice.

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You could do the test now and this test is usually done by

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sends a sample to the laboratory and it is not obvious to the doctor, to the attending physician and to the patient that the laboratory is actually producing a C.E.

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marked test, C.E.I.V.D.

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or whether it is a self-production of the laboratory.

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This is, so to speak, non-transparent, and the European Commission or the European legislator has recognised this situation and has also set it out in its recitals, that the highest possible level of health protection is required.

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and that in this context it is essential to tighten up the in-house production of health care facilities.

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Is it still allowed at all or is it comparable to the M?

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D.

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R., where it says if there is commercial C. on the market.

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E.

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is that you are no longer allowed to make your own products at all.

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Yes, this is exactly what it is aimed at.

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Because the I.V.D.R.

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in the recitals then also shows that it is precisely insofar as there is corresponding C.E.

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There are marked products on the market that achieve the same level of performance, so that there is no legal basis for a Lab Develop Test.

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So, it must always be a product that meets the needs of patient target groups, so I can quote it,

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have to be satisfied, then the justification is there that a Lab Develop test can still be placed on the market, or it is not put on the market, but only offered.

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Of course, this has quite a business impact.

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I think we'll talk about it more later.

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But now maybe back again, assuming that the lab decides now and has the opportunity to develop a Lab Develop Test, what are the requirements that

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the I.V.D.E.R.

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these L.D.T.s and how do they perhaps differ from the requirements that other manufacturers of C.E.

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labeled products.

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Yes, to what extent they have distanced themselves from the C.E.I.V.D.

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marked products, I might want to put it on the back burner.

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There are a whole series of requirements that are now mentioned in the I.V.D.R., namely in Article 5, there in Section 5, there are a whole 9 requirements,

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which are now specifically mentioned and which are primarily based on the fact that one wants to restrict the commercial status to a certain extent.

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It says that the products may not be given to other institutions, although one still has to define what other institutions are.

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So in other words, is this a different company, an independent entity?

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There are many laboratories that are also part of a merger, but there is still a lack of guidance or concrete formulations, which the IVD offers

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He doesn't.

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Then the second point is that you have to have a QM system that is suitable for production and you have to be careful not to fall into the misjudgement that such a QM system, which is usually also available in the laboratories, is usually even accredited according to ISO 15189, that it does not contain any aspects of production and therefore the QM system must be expanded in any case.

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The third point,

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is that the laboratory must definitely be accredited according to this ISO 15189, whereby national regulations are also allowed and we have already clarified this.

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In principle, this is the requirement of the guideline of the German Medical Association for the

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Quality assurance in laboratory medicine and this national regulation will then also apply equivalently.

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So this would be sufficient, although of course ISO 15189 would be the right standard on an international level in Europe.

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And then, as a fourth point, there is this particularly critical requirement that it must be justified in writing that there is no similarly suitable C.

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marked product on the market.

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And that is probably the sticking point that really has to be ensured so that you are not legally vulnerable.

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The fifth point is that the manufacturers or the laboratory in-house developments, they have to provide documents in this context, whereby

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the manufacturer does not have to apply the same specifications as a CE-IVD manufacturer, i.e. technical documentation is not mentioned here, but the IVDR does not specify more precisely what this documentation must look like.

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So in case of doubt, you have to assume that if you work according to the state of the art

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is that you have to present technical documentation here and be able to transmit it to the authority at any time.

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And that makes us relatively comparable to the M. again.

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D.

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R., because there we also have the requirement for a Q.

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M.

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system.

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There we also had the requirement that the essential requirements must be substantially proven.

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I have now heard 2 differences.

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One is that you need this explicit justification again and the second is a special feature that many laboratories already have

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accredited or certified Q.

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M.

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systems, but that the scope of this Q.

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M.

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systems for development does not cover this development at all.

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Did I understand that correctly?

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Yes, that's still the difficulty.

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You have now spoken of development, explicitly one speaks here of production.

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They, they therefore go into very little detail about the development.

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Another point that is formulated as a requirement is the concrete interpretation

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of the products.

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So here you also need design documentation and in my opinion this is only available if you have a compliant development process and can represent it.

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So this is also indirectly required.

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K., so now we've talked about the requirement.

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What would you recommend in the laboratory that has a Lab Develop Test, which would now be under some kind of self-production, what would be your recommendations on how they should proceed now so that they

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if the I.V.D.R.

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are also willing and actually comply with this regulation.

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So in principle, there is no way around the Q.M.

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system to the extent that development and production can be mapped well.

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As a rule, these are not extreme development processes of highly complex products.

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They are often products that are modified in a certain way, where perhaps for a P.C.A.

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Assay Primer

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and probes.

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This is not an insane development step that needs to be documented.

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From this point of view, it is a manageable effort to expand the QM system so that it fulfills a few aspects of ISO 13.485, i.e. the standard for manufacturers and to supplement it accordingly.

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What you then need are processes to

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To create files, i.e. to generate at least large parts of the technical documentation, and this should of course be appropriate in terms of scope for such a laboratory-developed test, so.

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let's put it this way, maybe a slimmed-down version of the technical documentation that definitely meets these requirements and clearly shows that you have met Appendix 1, i.e. the basic safety and performance requirements.

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So 2 big construction sites, Q.

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M.

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system, you say it's a finite thing.

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The second is to create the technical documentation.

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I suspect that this technical documentation

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must also include all the proof of performance.

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Is that correct?

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Yes, exactly.

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So the performance evaluation is of course the biggest chunk that the IVDR generally demands for manufacturers.

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And now the point is, to what extent does this apply to the Laboratory Develop tests?

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And I would say that because of course part of the performance evaluation is also the clinical performance evaluation and is also mentioned there as an element that data from the

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of the routine of a clinical laboratory can also be used for performance evaluation, I would now assume that the laboratories for their own Lab Develop tests can of course generate the clinical data very easily.

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And in this respect, it should be very easy for laboratories to substantiate the performance data accordingly.

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Of course, the extent to which you then have to meet the complete requirements of the IVDR in this regard has not yet been clearly regulated.

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There is a lack of any guidance.

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how laboratories have to deal with the demands of the IVDA in such situations.

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But it is also a requirement that the performance data must be presented according to this Article 5.

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In this respect, you can't make any significant compromises.

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It is important to meet the 3 essential building blocks of performance evaluation: the Scientific Validity of the Analyte, i.e. the scientific validity of the analyte, the analytical performance.

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and clinical performance, these 3 building blocks should be documented.

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It sounds as if the hurdles for the in-house manufacturers, i.e. the laboratories that carry out these Lab Develop tests, are not as much lower as those for the manufacturers themselves of products that are actually placed on the market.

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How long will something like this take or how much does a laboratory cost to meet the requirements of the I.V.D.R.

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to comply with the

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Which are placed on these self-made products.

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Yes, of course, it essentially depends on how complex the products are and how many of them there are.

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But I'll say that there are certainly a lot of synergistic effects.

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when you now have many similar products.

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So now just to draw a comparison to the generic product groups, that would be an idea of how you could do that, let's say, for many products in one line.

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However, a five-digit amount is certainly necessary for setting up such a category or a single Laboratory Develop test, which you have to plan for, and this could also go into the middle ranges if complex products are required.

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that would be the rough estimate I would make from the experience we have with I.V.D.

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manufacturers, if you can save something at one point or another.

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And how long will it take if you now refer to these same experiences again?

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Yes, the big problem here is that in the analysis of the role that is involved, we

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find the problem in such laboratories that there is usually no regulatory affairs expert, but that is usually always the quality management managers who do not yet know this topic of regulatory affairs as is perhaps the case with manufacturers.

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That means that I actually see a training issue in the laboratories or maybe even the hiring of resources to really get it done, because dealing with such productions

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development and development-related norms are usually not yet in place.

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There may be exceptions, but that's the experience we're having.

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That's why it's difficult for me to estimate how long it will take.

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But I'll say that less than half a year or better three quarters of a year is out of the question, especially if these basic requirements of the training are not yet met.

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So if you want to create this plan or this project plan, we have 2 parts to consider.

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First of all, the resources,

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To procure, i.e. people who are able to know these regular ones, to implement them and the second part then really do that.

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You spoke earlier about building a QM system, creating technical documentation and then also carrying out this performance evaluation.

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And then the question arises, is it still worthwhile for such a laboratory?

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The decision must now actually be made by each laboratory as to when it will pay off.

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Of course, there are certainly laboratories that also specialize in rare diseases.

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Of course, it would be an extreme shame and perhaps even regrettable for society and for our health care system if we were to abandon such patients now.

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So in the end there is also the

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Legislators are calling for corrections to be made again if the law now punishes those who take care of such patient groups too harshly.

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So what is definitely no longer possible, in contrast, is that a laboratory in principle.

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A CE IVD manufacturer competes by offering a self-developed test that does exactly the same thing as a CE marked test.

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Just because you know that you are not subject to the strict monitoring by notified bodies, you can of course save costs.

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And even in terms of development intensity, leaner paths could theoretically be taken, but this would not guarantee the same state of the art.

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And there I clearly see the

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that this competition with each other is not expedient here and that the laboratories should concentrate on it.

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OK, so what are the tests that are actually not offered by the market and pounce on it?

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The danger, of course, is that at some point a.

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manufacturer around the corner, could also be a competing laboratory that comes up with the idea, well then I'll just make a CE marked test out of it, because I have the data.

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And that's the big danger, if you then develop into such a Lab Develop Test, that the whole thing could suddenly tip over and the legal basis for offering an L.D.T.

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is compromised by the fact that another

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the C.

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E.

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product with the same performance data to the market.

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And that's what you have to keep in mind and, in case of doubt, be prepared to use the C.

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E.

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or perhaps even in anticipatory obedience to do so for the product that brings in the most sales and is in danger of being labeled as C.

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E.

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marked product is placed on the market by another supplier.

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This means that the

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competitive situation reversed in a way.

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Previously, laboratories could use these in-house productions to produce the C.

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E.

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by not being subject to the same regulations and possibly being able to offer the low-priced one.

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Now it's turning around, they can only do that as long as there is no C.

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marked product on the market.

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And you just said that of course it poses a certain risk.

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This means that if you want to avoid this risk, it would be quite helpful to

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that one continues on this path and not only fulfills the requirement of this Article 5, but then actually also a C.

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marking.

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One sentence that I also think is particularly remarkable, which you just said, is that it is ultimately about developing high-performance products for our healthcare system, developing safe products.

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And for this reason, on the one hand, it is good that the

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We have raised the bar a little higher for laboratories, which have not been so strictly regulated so far, but on the other hand we must also avoid at all costs that patients are undersupplied because patients, because laboratories can no longer meet this requirement.

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And it should never come to that, and we at the John Institute would definitely like to make our contribution.

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So we also help small laboratories, sometimes free of charge, for example our Micro Consulting,

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My recommendation would be, take advantage of this, use the specialist articles, which we also link to below this podcast.

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And if we can help you to place your product on the market in accordance with this Article 5 or even in the sense of a manufacturer, then let us know.

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We are looking forward to it.

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Sebastian, thank you very much for this interview and see you soon.

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Thank you, Christian.