Johner Institute

Computer-based modelling and simulation for medical devices

With Jan Hertwig, 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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Last week I was allowed to give a lecture with Jan Hertwig, even the keynote at Medconf on the topic

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Computer-based modeling and simulation in medical devices.

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Some were unable to participate and that's why I wanted to go through the most important points again today with Jan Hertwig and show how simulations can help manufacturers, especially medical devices, to develop their products faster, to verify and validate them more easily and quickly, and to get them through approval.

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Yes, and there I have Jan Hertwig with me now.

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Did you want to introduce yourself very briefly, Mr. Hertwig?

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Thank you very much for the invitation.

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Yes, I'm Jan Hertwig from Katfirm Medical G.

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We deal with simulations of medicine and medical technology with Katfirm Medical, I studied medical technology myself from a background and came to Katfirm Medical more in the direction of plastics technology and then in the direction of simulation.

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This means that simulation and computer-based modeling is now an integral part of your work.

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What exactly does this mean, this computer-based modeling and simulation?

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Under computer-based modeling and simulation, F.E.M. is usually created.

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or C.F.D.

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Methods, i.e. finite elements or computational fluid dynamics, i.e. a problem, a physical problem, which is divided into small finite elements, which can be calculated again with classical static-mechanical methods.

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And that's a method that is definitely used in industry, automotive and nuclear technology, as well as aerospace,

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and is established there to represent and analyze physical processes and to understand them better and then to represent and analyze strength, vibration behavior or crash behavior.

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Now, of course, we are not in nuclear medicine here, but in medical devices.

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We now have other questions, in the end it is always about the fact that we have to prove that the medical devices are safe, that they deliver the promised performance, that they meet the clinical

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benefit.

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So you can use it, for example, to prove the stability of a product, but also to find out how a person interacts with a medical device.

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We had an example at Medcon, for example, of how a dialysis patient reacts when the fluid is ultrafiltered to him.

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Or another example we had was a

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3D mammography, where you just wanted to find out how powerful, how good these images are.

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And the interesting thing was that these images had been completely generated.

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So then both the mother, i.e. the female breast, and the device have to simulate.

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What advantages do you expect from this computer-based modeling and simulation?

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And maybe we can first look at the other domains and then go back in the direction of medical devices.

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and who could perhaps learn something from the other domains?

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Exactly, so simulation is also classically used in product development, or also in approval, also in other sectors such as automotive or trucks, crash tests,

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simulatively and no longer in reality.

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The same will certainly take place in medicine and in this context computer modeling and simulation in the context of medicine and medical devices in the future.

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That is, for the approval of medical devices or really depiction of medical processes in the patient or during treatment.

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So, for example, this new term, which has also been introduced here, already insilico, that is, from in vivo in vitro insilico

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just refers to the fact that processes are analyzed in the computer, i.e. then calculated in silicon and the

experiments are carried out there, and this will certainly be available in the future for computer models of cells, organs or subsystems of patients, virtual synthetic patients for testing medical products and digital twins of organs, i.e. organs as a service, and these

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then simulative clinical trials, i.e. in silico clinical trials, which can be carried out here, with various ethical advantages, i.e. reduction of animal experiments, reduction of benchtop tests, better understanding of products, how they work, in patients, as they themselves.

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on a benchtop.

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So that you don't just have the benchtop as a result, it breaks, I also understand why it breaks or why it doesn't work well in the patient, doesn't perform well and also a record for post-market surveillance, so really objectively collected data, which can be evaluated later when it's in the field, in clinical use and of course then at the end of the return on investment, that you simply take time with the clinical trials and also with the approval of

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Medical device saves.

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These are the striking advantages here, I think, of Insilico or computer-based modeling and simulation.

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So these are 2 big classes, if I understood correctly.

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One is simply everything that has to do with effort, costs, speed, development, verification, validation and approval.

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And the other thing you just talked about is the ethical aspect, that you can use animal experiments, but also human experiments, i.e.

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clinical trials, but they are significantly reduced in number, in duration.

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And that is exactly what the F.D.A.

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has set itself the goal of bringing down this number of clinical trials through Incilico Clinical Trials.

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And as you said, to do this, you have to map the medical devices and their interaction to people as well

as possible in the computer

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to be able to try things out.

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I think you have just touched on another aspect, namely that we can also try things out in these Incilico Clinical Trials that could not be tried out in real life for ethical reasons.

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For example, setting parameters that might not be particularly helpful for humans or exposing the device to loads that would otherwise become a danger to the patient.

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a subordinate clause has already appeared a bit, the term as a service, namely with the organ, you had mentioned that, if I am correctly informed, you do something like that at Cutfirm Medical.

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So, what are these services in the field of computer-based modeling and simulation that you offer and what benefits do manufacturers who use and access something like this have?

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At Cutfirm Medical, it's a lot, we, we develop medical devices ourselves, that is, we develop,

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Medical devices where simulation is used for therapy, planning, and diagnosis.

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In addition, we also make so-called M.D.D.T.s, i.e. Medical Device Development Tools.

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This means that you provide a service or an organ as a service, so to speak, or a part of a digital twin, a patient, in order to examine and test medical devices on it.

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these are the topics, let's say, that go very far into the future, but are already being applied now.

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If you start a little lower, they are also classic contract calculations, simply to support the approval of medical devices.

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This means worst case assessments, post market surveillance and testing of batch size 1 products, i.e. custom implants et cetera, that you can simply offer digital verification.

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and also geometric fitting studies and expansion of patients are possible here.

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So there are various service offerings all the way up to seminars, where we also show how the standards and guidelines can be applied in order to approve or approve medical devices with simulation more quickly and and and, for example, to reduce bench-top tests or to expand clinical trials and expand cohorts.

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That is, what you bring with you,

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is a lot of preparatory work that they have done in order to have to prepare products, parts of products or organs, as you just said, the models for them, which is of course an extremely large amount of work.

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In other words, not only to develop the models, but also to validate these models.

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And that may already lead to the next aspect, namely the question of what regulatory requirements do we have?

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Yes, maybe we can divide them into 2 parts again

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On the one hand, we have the regulatory requirements that the products have to meet, i.e. in Europe, the classic basic safety and performance requirements.

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But we may also have requirements for the verification and validation of the products, i.e. for the methods we use for this.

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And since we want to use modeling, as you just said, as a method of verification and validation, we also have to consider, yes

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What regulatory requirements do these models have to meet?

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And if you ever see the M.D.R.I.V.D.R.

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studied more closely, he won't find that much there.

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Although it requires a justification for the chosen solutions, i.e. for the chosen design of the product, it does not really require a justification for the choice of method to prove that the basic safety and performance requirements are met.

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However, Appendix 2 clearly states that

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that these methods must be explained, that it must therefore be transparent when you have done so.

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And we also find many indications in the MDR that we are explicitly allowed to provide this evidence with computer models, with simulations.

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So, you definitely have explicit permission, but no concrete requirements for the validation of these models.

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If you keep looking, you will come across 13 485,

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requirements are certainly relevant, such as computerized system validation and these models and are also computer systems, so they certainly fall down there.

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We have issues such as DIN or requirements for process validations, for the validation of measuring equipment and so on.

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So it is said that we are not in the regulatory free area here, but we do not find very specific things in Europe now.

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in the U.S.A., if we change the side of the Atlantic now, we will find a little more.

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The F.D.A., which is also actively promoting this topic of computer-based modeling and simulation, has written some scientific articles, but also explicitly says that they want to develop this modeling from the corner of the scientific tool towards the regulatory tool.

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for example, they have published a guidance document that describes how they would expect computer models to be documented or validation using computer models.

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A document from the American Society for Mechanical Engineering, the Verification Validation Four T, is even more precise.

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40 that the F.D.A.

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also explicitly referenced

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and there it is much more precise.

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Hertwig, could you give us a very brief rough insight into this document, what this asthma V.N.V.

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Forty from manufacturers who want to use computer-based modeling and simulation in medical devices.

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I'll try it very briefly to see if I can summarize it.

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Also die V.N.V.

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Forty is ultimately a risk-based approach,

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to assess how much verification and validation is necessary for a computer model, always depending on the risk of the decisions made with the model.

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That is, how high is the influence or consequence of my computer model at the time of approval, how much verification and validation must then be carried out according to this risk and this influence.

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And the authors have done this very well

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summarized in a very nice plan, I think, so the and in a very nice document to prove that the model is reliable and that the model makes a reliable statement.

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And without verification and validation, it is also not possible in medicine and also in simulation.

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So you always have to verify and validate and also these models, the decisions you make with them and the A.S.M.E.W.

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and V.V., which describes exactly how much verification and validation lead

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certain computer model is necessary.

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Yes, and interestingly enough, very, very detailed, at least for me it was interesting.

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But I would like to emphasise what you have just said, namely that it is a risk-based approach and they have said that these risks depend on the consequence of this model, for example whether the results are used directly or whether they are used again

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are checked with further tests, so to speak, one dimension and the second dimension are the consequences of this decision, i.e. the degrees of severity.

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And of course, the higher the influence of the model on the decision and the more critical the decision is, the higher the requirements for the verification or validation of this model.

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And I found it interesting how exactly they go through it.

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So really from, for example, the proof of the model of the comparators, the measurement of the comparators, with which it is compared.

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So an example of comparator would be that you showed me, if we simulate a bone, for example, the comparator would probably be the bone of a corpse that might be used for stress testing.

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They demand that we use classic software quality assurance.

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Of course, we take a closer look at discretization errors.

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So for those who are active in this area, I think it is an extremely precise specification and yes, one wishes that we in Europe would have similar efforts and similar successes of our authorities and notified

bodies in pushing ahead with such regulatory requirements.

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What do you think, Mr. Hertwig, what are

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the most important requirements that a manufacturer must meet in order to benefit from these advantages of computer-based modeling and simulation.

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I think the most important prerequisites are qualified personnel, i.e. experts, simulation experts, who are also familiar with the context of

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Feeling comfortable and familiar with medicine and medical technology, i.e. also being able to live with risk-based approaches, dealing well with technology simulation, also having a good basis and basic understanding of it.

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So these are simulations at the highest level with of course also risk and consequences.

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That is,

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for the approval, for the safety of medical devices.

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So it takes an education, a very good training and also a training on the methods, i.e. V.

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and V.

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Forty and the Guidances et cetera, that you can get really meaningful models with good verification models and good decisions.

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I think that's an important prerequisite and just like the software tools that you can also use them in your

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13485 216 also performs the computer system validation accordingly and then you can really always use it nicely.

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And certainly an investment is necessary at the beginning, but it also has a nice return on investment by

bringing your medical devices to market quickly or really saving time and money during approval and thus taking away a huge pain from medical device manufacturers.

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How long did it take you to delve into this topic?

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so that they can work at this altitude, which then allows them to really be able to act more purposefully in terms of development, of certification.

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Well, I think in the Cut for Medical we have been very active on the topic since 2015, so for a relatively long time.

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I, too, have dealt with it full-time, or many and my colleagues have dealt with it, also with all the regulations, all the regulations,

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have just been created, so the VNV Forty is also from 2018 and that means they are still in progress.

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That means it's still a bit fluid, the U.

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is already very far along, but this incorporation of these new standards will then also be relatively fast.

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So once you have acquired the knowledge, such as the Cut for Medical, and passes it on, then it is also relatively quickly applicable knowledge for a simulation expert, i.e. someone who deals with it.

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is really familiar with the topics and then it is actually easy to apply, quickly applicable and quite clear and well formulated, as you have already said, the VNV Forti then also gives very good guidance on how this VNV has to be prepared by the model and then it all fits very, very well into the whole development process of medical devices.

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Assuming that a company has now invested in its own personnel or uses someone like you, for example, are there any other obstacles that

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You can see that prevent manufacturers from making use of these very fascinating possibilities to bring their products to market faster and safer.

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Yes, so I think a big obstacle is the regulatory ambiguity in Europe at the moment and that there is no real guidance for it or any applicable standards or any guidelines and also the problem is that all the Notified Bodies

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It's just organized differently than in the USA.

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The FDA was very, very advanced, recognized the potential of Insilico and reacted early.

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In Europe, the MDR has not yet reacted at all.

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That's why there are no regulations that are directly applicable to it, no Notified Body, because it is really.

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to deal with it, it is already used, simulation is also used in in in the approval already, but every notified body, every auditor applies it differently.

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So I think that's definitely the biggest obstacle and you have to work on it and that's what we're doing in with the A.W.

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Channel Alliance.

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I myself am also in the Working Group, Notified Bodies.

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We want to train the Notified Bodies and also show them, first of all, create awareness that this method exists and how to use this method correctly.

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and for this guidances must be created and this must be distributed across all Notified Bodies, if possible, or distributed so that not even one Notified Body is in the U.S.P.

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and can offer testing in silico.

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It must be available to everyone and everyone must be able to really apply this knowledge, simply apply it.

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So they are already in the middle of the field of regulatory science and the dream would be if you could then

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We could create similar guidelines, as we may have already done for other areas, i.e. artificial intelligence or I.

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Safety or if we could even raise it to the level of a standard, although the topic of standards is currently a somewhat unpleasant one.

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What do you think if a company now says, yes, I'll dare to do it now, I'll invest in it, what would be the biggest mistakes that this company should avoid at all costs?

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The biggest mistake, I think, is that you get carried away with a hype.

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So I think Insilico is a very research-related topic, it's certainly still a topic, it's an applicable topic in small pieces, but if you go too far now and if the hopes that are then placed on Insilico are not fulfilled and you just go too fast and then just do something wrong.

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So so, go, go to quick, end up being wrong, that would be the biggest problem that could happen in Silico.

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and perhaps an over-regulation, that you then create an over-regulation in the area through a scandal and look too closely at the methods and impose too much regulation on this new possibility.

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I think in medical technology, mechanical and physical testing is still somewhat unregulated in how an experiment is to be carried out, then in the last in a standard, i.e. in the benchstop test, for example, clinical studies is something different, but.

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with the bench tops, for example, there is also a relatively large amount of spare space, which is also ne-

cessary for the respective products and that this alternative space must also be available for in Silico.

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I see a bit of a risk of what could happen, that it will then suddenly be overregulated because mistakes are made due to hype or people act too quickly.

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And then we would have achieved exactly the opposite of what we want, namely to put safe products on the market more quickly.

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what do you think would be a good or good next step for a manufacturer to get involved in this topic and really benefit from this benefit?

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So good next steps for a manufacturer will definitely try to familiarize themselves with the topic, really look at the standards, the guidance is first and say, O.

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K., what is the straight step in the F.

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D.

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A., how can I also use this in my products and

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what is necessary to simply inform yourself and see where I can best use it and then as early as possible in a medical device development, when you develop a new product, set your budget for it and see that you, how can I now use for this specific product in silico and maybe just put it on a, 2 products and experience the advantages hands-on.

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It's certainly something that needs to be built up can't be done right away.

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you have to invest first, but I think that's the most important step, just to try, dare and try to implement it with the already existing guidance and standards.

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So here, too, the longest journey begins with the first step and many small first steps.

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I think the suggestion is really just the right one with the very specific product and a very concrete question regarding this product, to go on exactly this path.

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yes, there is much more you can tell, tell, describe about this topic.

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That's why, as always, we have linked you to an article and other sources in the description below.

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And of course, Hertwig and I are always ready to accompany you on this path.

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Contact details of Mr. Hertwig can be found below, the contact details of me, you know them anyway.

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So just get in touch, Mr. Hertwig.

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Thank you very much for being there.

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Thank you very much for the invitation, I was very pleased!