

the mating, during the gestation period. And also, for some subgroups we are doing postnatal vaccine administration. And we measure the IgG just to show that the species is answering to the vaccine.

So for me--and I hope that you will challenge this idea--in a tier one, we do immunological end points to justify the species selection and the protocol design. Only for that.

And we will do the study without immunotoxicology tests.

We mainly focus on classical teratology end points. We don't do cytokine measurement. We don't do functional assay by immunizing the animal with another antigen.

I should admit that we don't re-immunize the pups with the vaccine, because we know that maternal immunization will suppress during a certain period the answer of the pups to the same antigen. So we don't re-immunize the pups. It is mentioned in the guideline that we may have to re-immunize the pups. Until now, on the four studies we performed, we never did that. So perhaps it's something which should be modified. I don't totally agree with that, but it can be discussed.

Regarding the tier two, I would limit immunological end points to mechanistic investigations. And I have in mind

only one example, which is meninges-B polysaccharide vaccine. In this case, in addition to a classical reproductive toxicity study, you may want to do in vitro antibody binding to show that the antibody made by the vaccine can bind to fetal tissue.

In another study, you may want to show that your adjuvant, or your live virus, perhaps can trigger a cytokine change. But I would keep these investigations in very specific cases: only if we have some good evidence that the vaccine or the adjuvant can trigger some changes, and if we want to further explain these changes. But I would not do this very specific investigation in a first tier.

I will stop here, and I will let my colleagues from the panel or from the room comment on this proposal.

[Pause.]

DR. VAN DER LAAN: Shall I first give my statement, and then we have the general discussion?

DR. VERDIER: Yes. Go ahead.

#### DEVELOPMENTAL ENDPOINTS

PRESENTER: JAN-WILLEM VAN DER LAAN, PH.D.

DIRECTOR, PRECLINICAL ASSESSMENT GROUP,  
MEDICINES EVALUATION BOARD [RIVM], THE NETHERLANDS

DR. VAN DER LAAN: I have not prepared a presentation as the other chairpersons for the sessions. I have only one point that I specifically want to bring in the audience, and a point that we have discussed repeatedly in our European clubs--the Safety Working Party, and the Small Pox Working Party--early this year.

And I think it's important that reproductive toxicity testing is not a purpose in itself. And that's important. Vaccines are derived, by definition, from infectious agents that cause human diseases. And to get insight in the risk of vaccination during pregnancy, we can learn a lot from the clinical experience with the pathogen exposure.

So for the live viral vaccines, as influenza, rubella, the mumps, the measles, and variola, the human pox--there might be others--we can learn a lot from the epidemiology from the illness itself.

And then, we have to think about, if the complete market will market the specific vaccine, what will be the decision for the treating physician? And as the U.K. is part of Europe: To treat or not to treat? That's the question. And that depends on the situation. Sometimes, passive immunization during pregnancy is more important than giving

a vaccine. And we should that clinical background keep in our minds when we are discussing reproduction toxicity testing.

That's just another aspect. And with respect to the other developmental end points, just because of these types of examples we know the developmental effects of rubella and human pox. I think those are not based on the--And Dr. Holladay is not present here behind the table, but he explained that that type of effects might also be immunological effects. But those types of end points are, of course, still important in reproductive toxicity testing.

Anybody from the audience has any comments on these statements from Dr. Verdier or from me? Or anybody from the panel? Yes.

MS. SHEETS [In Audience]: Hi. I'm Rebecca Sheets. And I just want to be clear to everyone in the audience: I'm not longer at FDA. so I'm not speaking for FDA.

It is my impression that animal models--I mean, we've had a lot of discussion about what's a relevant animal model, and how difficult that's going to be. It's my impression that animal models are inherently imperfect, and they may or may

not be predictive of the human situation. So to expect the animal models to predict subtle effects, like the immunological effects, it's going to be asking too much of the animal models.

I think it's warranted to do these kinds of studies and to be looking for gross effects. And if you see such gross effects, then doing further studies in a second species or that sort of thing may be warranted. But I think the only way to get at these subtle kinds of effects is really going to be studying humans and epidemiology. And, yes, there's a lot of problems with doing epidemiological studies, as well.

But I think that it's asking too much of these imperfect animal models to be looking at very subtle, downstream effects that may or may not be seen, may or may not be able to be measured, and in the end may or may not be relevant. I think looking for the gross effects is really all we can ask of these animal models. So that's just my scientific opinion.

DR. VAN DER LAAN: Anyone from the panel? Marion?

DR. GRUBER: I'll hold my comments.

MR. PARKMAN [In Audience]: Hi. I'm Paul Parkman.

I listened all day yesterday and today. And it seems to me that from what I've heard, the evidence that past vaccines are toxic, either reproductively or developmentally, in a way that preclinical laboratory studies can help, is extremely rare. Rubella, of course, is one of them. It seems to me likely that the need for these tests is driven by the need to have something we can say in the packet circular about these matters. And given this, I think the most useful approaches might be two-fold. One is, in the unusual circumstance where there is some reason, from epidemiology or clinical medicine, to suggest concern--and rubella might be a classic example of that--then the sponsor should be required to develop studies that are tailored to answer the specific questions that are raised. And so some sort of screening test wouldn't be particularly applicable here.

For everything else, it seems to me that a toxicology test should be sufficient in one species, using the "best animal model"; recognizing that often the best model is probably not well defined.

But for these studies I would think probably reproductive toxicology would not be required, unless there was some new

and really convincing evidence of a certain need for them. That would be sort of my take on it. Thank you.

DR. VAN DER LAAN: Anybody, comment?

DR. GRUBER: Yes. I have a question for Dr. Parkman. How would you define evidence for the need of developmental toxicity studies in the absence of clinical and preclinical data?

DR. PARKMAN [In Audience]: Well, what I was referring to as evidence was evidence from epidemiological studies of the disease or a clinical study of the disease that suggested that the organism or organisms closely related to it had some reproductive effects that it was important to define.

DR. GRUBER: Well, thank you. That's, of course, one point of view: To have reproductive toxicity studies only for those types of products for which the "Y" type disease would suggest an untoward effect on fetal development. However, as we have been pointing out, we're really faced with a really novel area of vaccines, product classes, combinations of products, the introduction of novel adjuvants; that I think that we may be going down a dangerous path to really dismiss all these issues and just

look at "Y" type disease. But that is my personal opinion, and I guess that is something that we can discuss a little further.

PARTICIPANT [In Audience]: I think that one of the problems that the audience has been grappling with is this almost necessity to have one type of study fits all cases. In reality, we could look back and say with our history of vaccination we really have no history of reprotoxicological problems.

However, we're all very excited, because we're facing a whole new era and set of opportunities in developing vaccines. And we're trying many new approaches. Maybe in tailoring these guidelines and so on we have to take that into consideration, that in a situation where we're using live viruses, attenuated live viruses, one has to look about transfer.

If the goal is to use cytokines as adjuvants, then measurements of cytokines would be relevant. And maybe we really are going to have to consider this based on the different categories of vaccines that are going to be developed.

DR. VAN DER LAAN: Anyone to comment on this?

[No Response.]

DR. VAN DER LAAN: I think you gave a differentiation, but you have given maybe voice to the audience that you agree that we are going this way as regulatory authorities in setting up these guidelines, providing this guidance to the industry.

Are there other opinions in the audience not willing not follow this guidance?

MR. HOPKINSON [In Audience]: Hi. I'm Bob Hopkinson [ph], from DynPort Vaccine Company. I'm also no longer with the FDA.

I just wanted to comment. I don't have a strong opinion in this area, but just in the world of drugs where I was before, you talk about what are the implications in terms of the label with these studies.

And one area that comes to mind is the quinoline antimicrobials. Early on, multiple species tested, finding cartilage toxicity. Getting into the label--Products never being used in pediatric populations, or very infrequently being used, and the use essentially off-label for years. And it's only recently with resistant pneumococcal and other types of infections where FDA is being asked to

consider looking at pediatric studies and trying to get some additional information.

Epidemiology studies really can't be done if you've got something on the label related to an animal toxicity which may or may not be relevant. And so, just another thing to think about in terms of our thinking process. If we search for a species that may cause an effect and we find it, okay, then you have to decide, well, does that mean anything? And it may preclude actually getting any epidemiologic data, because no one is willing to use the product in a pediatric or gestational period.

DR. VAN DER LAAN: I think that that's indeed an important statement; that you can also abstain from giving a vaccination during pregnancy. But the problem is, as indicated by--

[Tape Change.]

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DR. VAN DER LAAN: --this risk assessment, where you can not always avoid it.

DR. CHRISTIAN: I wanted to say that I agree with your tiered approach. And I think that to look for specific end points that are functional without a reason, in an initial run-through, with no other effects, would be pushing the

model perhaps beyond what we can do at the first tier for screening.

But I believe that that first tier is important to do, because we don't have good data as a rule on the disease models themselves. And we're coming up with so many new things that it isn't just the immune response, which was what we were first looking at, if you could even define what we were considering an immune response; but rather, the multiplicity of the different types of agents that we're using.

And I don't think, or I hope nothing was interpreted as "There's only one way to do this." It's certainly a case-by-case basis, where the sponsor is responsible to figure out what they know about the compound and what's the most appropriate way to test it. And I think that's just axiomatic, and should not be forgotten.

Now, if they have a reason they think it is going to be immunotoxic or immunosuppressant, then you test for those things, just as you would if you thought it was CNS-selective and doing something there, or toxic to the liver or the kidney or something else. You would put in any

points that you wanted to look at to identify effects in the adults.

But I believe that ethically, before we go into pregnant women or have inadvertent exposure of pregnant women, we have to do the best test using the current tools that we have--admitting that they are inadequate; but they are still better than nothing.

DR. GRUBER: I couldn't agree more with your statement, Millie. And I really also wanted to say that I am supporting Francois' suggestion for the tiered approach that is no longer up on the screen.

The question, however, that I feel we somehow have to answer, coming back to what I said this morning--We wanted to hear comments; we wanted to address concerns raised by industry in response to us publishing this guidance document. At the end of this day I'd say: Are we back to the ICH as far as a guidance document? Do we need an additional document at this point?

So I see people shaking their heads, nodding. Jan, you wanted to say something?

DR. VAN DER LAAN: I think that vaccines are in their concept so different from conventional products that it

might be helpful to the industry to give guidance in addition to the reproductive toxicity testing document from the ICH.

I'm wondering why only at this point the FDA has made a guideline. But I would say, have a guidance document. And I have learned that you are preparing that for the development of vaccines.

I have a question also on the tier two to Ken Hastings. As we know, in the immunotoxicity discussions for the conventional product, we have given a first look at the developmental immunology of immunotoxicity testing; and in that way, a function test at day 21--day 20, 21, or the period of weaning.

What is your feeling? Should that be a standard approach for vaccine?

DR. HASTINGS: Actually, I was thinking about the one slide that Ralph showed, Bob Chapin's very complicated but nice repro-tox testing scheme. And it did have the immunotox end points.

As you know, in the immunotoxicology guidance we say that if you know that a compound is immunosuppressive and you know it's likely to be used in women who might become

pregnant while taking the drug, that there should be an evaluation and a repro-tox study, and basically we said a histologic examination of immune-related tissues. And we kind of left it at that.

And the reason for that was that we felt like when we were writing the guidance that there wasn't enough information to make a recommendation about a functional assay. Now, Ralph and some other folks have actually worked very hard to develop these functional assays to be incorporated into repro-tox studies. And I would like to see a lot more work, or some more work, done to that, so that maybe we could make that recommendation.

And I think that the work that Ralph and Greg Ladix [ph] and some other folks have done purports, you know--I won't use the term "validated," because that's a heavily weighted term. But where we could feel more comfortable about that, then, yes, then at that point I would like to see that incorporated. And we probably would change the guidance at that point.

Did I answer your question, Jan-Willem? Yes.

MR. RUSSO [In Audience]: I'm [inaudible] Russo, of Merck.

I'm not sure that I understand the logic behind that. Because you say if you have any reason to believe that the drug that you are developing is immunosuppressive, then you do this recommendation. I guess it's because you want to assess whether or not this temporary immune suppression will affect the fetus by exposure to viruses or microbiological agents. Is this really relevant to vaccines?

DR. VAN DER LAAN: May I give that question to Francois? Do you expect that you ever will apply the second tier testing?

DR. VERDIER: I would not include a functional test like suggested by Ken. Sorry, Ken.

DR. HASTINGS: That's all right.

[Laughter.]

DR. VERDIER: I think at this stage we want to have some gross evaluation of the vaccination on the pregnancy. It seems that we are in a totally different situation compared to chemicals which can trigger an immunosuppression. So I would be cautious about adding functional tests at this stage.

And that's why also, I think I was clear in my presentation, I would not re-immunize the pups with the same vaccine. Because I think this can be misleading. We will observe a suppression of the B cell response, and some people may think that it's an immunosuppression. In fact, it's not an immunosuppression; it's a normal effect of vaccination of pregnant animals or pregnant women. So I would avoid to add either an immunization with the same antigen, or I would avoid also to add function assays. But that's my very personal opinion. I think it's the opinion, also, of my colleagues from Merck. Perhaps in 20 years we will have a different opinion, but today that's it.

DR. VAN DER LAAN: Thanks.

Marion?

DR. GRUBER: Yes. I just wanted to make one comment, and I think that is an FDA comment. If you read the draft guidance, I think the issue of re-immunizing pups to further look at potential for immune suppression is something that even the guidance document did not really support.

We really said that these types of issues may need to be addressed clinically. And as a matter of fact, there are instances for maternal immunization studies where the potential for an immune suppression in infants is addressed clinically because we didn't feel that the animal models would really give you the answer to that question.

DR. CHRISTIAN: Just a comment on your question of: Do you need guidance other than ICH? I think the real problem is that the ICH guidance covers everything, but here we're not looking at a standard type of response. Because we're really testing the effect of an immune response on the pregnancy, rather than in combination with an adjuvant or whatever other things that are in this particular vaccine. And it would be helpful, because these groups generally could use the guidance. And it would save you some telephone calls, perhaps. And they would have it in better order when they come to see you, because they'd have guidance; rather than saying, "Oh, I'm going to do it every day because that's what's appropriate for a developmental tox study," or, "I don't know that I should look to see whether it crosses the placenta," and so forth.

So I think the guidance document would be helpful, particularly because there are so many new companies that are coming along; where the large companies, they've got their programs in order, but the small companies need some guidance.

PARTICIPANT [In Audience]: [Inaudible] from NTI Research. I'm a veterinary pathologist.

And going back on the same topic of going back to the ICH guidelines, I would like to hear some rationale for actually even measuring antibodies on the mother and the pups or in the milk. As a pathologist, if you're concerned with the adverse effects of antibodies or toxicity, and not efficacy, but if you're concerned with toxicity of antibodies you would look for effects in the fetus by histopathology or post-weaning. So you do multiple time points. Because just measuring antibodies won't tell you anything.

And I'm seeing myself writing a report of antibody levels and going, "Okay, there's antibodies in the serum of the dam, there's antibodies in the serum of the fetus--" Or, "There's no antibodies in the serum of the fetus." What do you do with that data?

You know, I understand Dr. Verdier's point of, okay, you're proving that you're inducing antibodies and the antibodies are actually passing to the fetus. But it's almost like a given. I know you don't assume anything, but you get a rabbit, that is expected that 100 percent of antibodies in the serum of them will pass to the fetus. I still don't see what you do with that data.

Okay, let's say you look at--And then there's antibodies positioned in the tissue of the fetus. If there's no damage, what do you do with that data? So I think I keep going back, and I don't see a reason, unless anybody can give me a better rationale for that.

DR. BARROW: Just to make sure I've understood, if you don't advocate looking at antibody titres, what other measure of exposure would you use?

PARTICIPANT [In Audience]: Well, you have all the data. You have your efficacy data showing that you can induce antibodies in adult animals, right? And so I'm basically just assuming that if you have a 100-percent transfer of antibodies, it's a passive transfer; it's not an active process.

DR. BARROW: It is an active transfer. It will depend on your vaccine in question.

PARTICIPANT [In Audience]: Okay. So I guess you could use that to prove, but I still don't see in the end what you do with the data. Like, okay, we proved that it did transfer. And what if it doesn't transfer? Then you have to re-immunize to make sure that you have antibodies in the fetus?

DR. BARROW: If we suspect there will be exposure in the human, yes.

PARTICIPANT [In Audience]: Okay. Thanks.

PARTICIPANT [In Audience]: Are we worried about the exposure to the antibody, or the intended immunologic consequence of the immunization? Or are we trying to assess the toxicity associated with activation of the immune system and what effect it will have on the conceptus, on the dam carrying the fetus to term, those kinds of questions? Those are two different things. We're talking about inadvertent immunization of a pregnant woman at some point in pregnancy. I don't know whether you should be doing the immunization during gestation. The issue is--

DR. BARROW: No, that is a--I'm sorry, can I just interrupt?

PARTICIPANT [In Audience]: Yes.

DR. BARROW: That's a consequence of the different gestation lengths between human and animal. We have to vaccinate--

PARTICIPANT [In Audience]: But the question is the effect of, let's say, the cytokine milieu after immunization. That should be done during gestation. And the primary cytokine milieu from a primary challenge may be different than a secondary challenge.

So I understand. Measuring IgG, and that tells you that that species can make an antibody response. And if you're worried about whether that antibody is going to cross and cross-react with some fetal tissue, that's a question, and certainly that makes sense.

But if you're worried about inadvertent administration to a pregnant woman, that's a different question. Then we can go down the path of saying, oh, it could be different on any given day of gestation. And then none of these models really address that question. So I'm still back at: What is the question?

DR. CHRISTIAN: I think Paul will probably back this up. The idea of getting to the maximum insult, the maximum exposure, and to have that over the extended period of gestation, at least from implantation to, let's say, the end of the fetal period, that's to address inadvertent exposure, by having that maximum response over all of those different days.

The only other way to do it is to do it on each of those days, which is the approach sometimes taken when you have two or three days, and then you do it another time during gestation, and two or three days. The other question, though, is if it's intended exposure. And that's a different case.

PARTICIPANT [In Audience]: Well, intended exposure if it's during--You know, again, the primary should be given during? You may do another arm where--

DR. CHRISTIAN: Yes.

PARTICIPANT [In Audience]: I think the GSK person mentioned doing where they immunize prior to, and then have another group where they do it on day six only. That seemed like a reasonable model approach to me, also.

But inadvertent administration--Again, are we worried about the intended consequence, the high-antibody titre and its effects on the fetus? Are we worried about the bystander effect of the adjuvant and the hyper-immune response that we're trying to induce to get that antibody response?

DR. VERDIER: I think we worry about both. My first feeling is that the first risk is an interaction with an immunostimulation which would trigger something abnormal in the pregnancy status. That's my first fear.

But in some cases, perhaps very rare cases, antibodies can perhaps have a harmful effect, as is the case--question mark--with perhaps meninges-B polysaccharide vaccine, even if we have never been able to show any relation with these antibodies.

DR. VAN DER LAAN: May I add a question in this respect? Do we need really the measurement of the antibody in the fetus? If we know, based on the data that Paul has shown and data known from literature, that certain types of IgG will cross the placenta, the industry has to prove that every time again, if there is no further consequence to be expected?

DR. BARROW: I think we need that data to justify our choice of species. As you saw with the data I presented, with different vaccines we did find different levels of maternal antibody transfer. So we used that data to justify our choice of species for the main study.

PARTICIPANT [In Audience]: I have actually a very provocative question. When I think about the inadvertent administration and the reality that the animal studies-- Basically, animals lie, and you can't really rely on a lot of the data that you get from animals.

So the provocative question is: Is the information that you're going to get from the animals more relevant or more useful than the information you would get from the pregnancy registries? And maybe the pregnancy registries should be something that is pushed more. Very provocative question.

DR. VAN DER LAAN: Very provocative. Who wants to give a first response?

DR. GRUEER: I would like to give a response. I don't think that this question is provocative at all. I really think that we need both assessments. I really don't think that we can do away with developmental toxicity studies and

wait until we have exposed pregnant women to get pregnancy registry data. I think we have to attempt to address the potential for any adverse effects of the vaccine induced in a potential pregnancy situation with all methods that are available to us. And in my opinion, that includes preclinical studies.

DR. VAN DER LAAN: I will add to that that, indeed, in this way, as a company, you are requesting for every physician treating pregnant women to do an NS1 study, without any control. So that's the real background.

We have to be aware of the fact that we are not developing guidelines for the old products that are reasonably well characterized thus far. But we are developing or writing guidelines for products which in many cases are recombinant vaccines or genetically changed, and that type of stuff. So you first have to characterize that type of risk. And it's not very ethical to do that directly into humans.

MR. THOMAS [In Audience]: Larry Thomas, Avant Immunotherapeutics.

A lot of the discussion has centered on the assumption of a per enteral vaccine. I was just curious about the feeling of the panel on if there would be any expectation of

different end points or design for a mucosal vaccine?

Assuming of course that there is a case-by-case assessment.

DR. VAN DER LAAN: Who will take this question?

DR. GRUBER: I don't have an answer. I can just tell you that we're going to be discussing this question, if we should really be requiring developmental toxicity studies for vaccines that are mucosally administered. We'll be discussing that, but we haven't really been arriving at a conclusion.

I guess the point, again, is made, you may have a mucosal exposure, but you may also then get systemic exposure. And again, you will have a systemic immune response induced. And so I think you can make a case for requesting a developmental toxicity study.

But I think that goes a little bit into the area that I don't think that we can really discuss here. But I think there is one question that the agency also has to discuss. And it is really taking another look to say, "Do we really need it for every product? Or could there be cases where there are exceptions to the rules?" And I think we need to discuss it. But at this point, I don't think there is any regulatory stance that I could give you.

MS. HOLMAN [In Audience]: Lisa Holman [ph], from  
GlaxoSmithKline.

Yesterday I asked a question about multiplasmid vaccines. And I was told that for toxicity testing we would need to consider those individually. Well, for repro-tox, when we look at recombinant vaccines and live viral vaccines, what we're looking at is the mixture of epitopes, maybe T cell epitopes. And we mount a polyclonal humoral response. If our developmental studies focus more on the immune response for multi-component DNA vaccines where we are going to mount a cell-mediated immune response to a variety of different T cell epitopes and the polyclonal response, isn't it more relevant to look at it as a whole product when we are looking at antigenic competition; and take Francois' tiered approach, that if we do see something with the combination product, that we then go back and look at it mechanistically in a single plasmid situation? Could the panel comment on that?

DR. VAN DER LAAN: Who is taking this question? Francois?

DR. VERDIER: For me, it's quite obvious that we are testing the final vaccine with the adjuvant with a

different component of the vaccine. And then, if we find something, we can go further. That's all I can say.

DR. GRUBER: Yes. I would have to think about this a little further. And I don't know if--I probably don't have a good answer here right now. But in a way, I mean, why are the issues so different at that point? Maybe I just don't understand your question right. But, yes, I don't know.

DR. VAN DER LAAN: Can you give why your problem is different from what we have handled thus far?

MS. HOLMAN [In Audience]: Well, I tend to think that there is a case for actually testing the whole vaccine in a repro study. But I guess I'm answering my own question in that, if I were to ask the question of were we going to have to do repro-tox on separate plasmids.

The question yesterday was we're going to have to do repeat-dose toxicity on separate plasmids, even though they're going to only be administered, ever, in a single product. So with the answer to that question yesterday, I'm guessing that the response will be that they will want individual plasmid repro-tox data. And I don't think it's relevant to generate that. So I'm asking you to consider

whether, as a repro-tox panel, you think it's appropriate to test them separately, or as a combination product.

DR. VAN DER LAAN: Is that a different answer? I would suggest that we should know more from this product, to give a more precise answer. Apparently, you have some of your concept in your mind that's not easy to explain in this way.

DR. GRUBER: That's perhaps true. And please, do not take this as a regulatory position, but if you are required--and we heard this yesterday--to do separate preclinical studies to evaluate the safety of the plasmid [inaudible] and then the plasmid containing the antigen or genes for the antigen of interest, you have already then that battery of preclinical data. And so then it would be conceivable to me that you can go into the reproductive toxicity study with your full product, because you have the other preclinical data. Okay? But you know, this is a very novel question. And we will take this into consideration.

MS. HOLMAN [In Audience]: Thank you.

DR. VAN DER LAAN: There were two questions there. Yes.

PARTICIPANT [In Audience]: Yes. Regarding the registry, I think that can be done as part of the clinical development.

So as we do at Merck during the development, we collect data in pregnancy, and that can be used at the end before licensure to provide and list the initial database on that. The second comment is regarding your question of whether or not we should measure antibodies in the fetus. And I'm not convinced of the relevance of any animal model that we're going to use. And so I don't really know how we're going to extrapolate the data you're going to get in any animal model to what's going to happen to people. And so, I'm not sure this is going to help you at all.

DR. GRUBER: Can I give this a shot?

DR. VAN DER LAAN: Yes.

DR. GRUBER: I think when we wrote the guidance and we said you should evaluate, or you should look for antibodies in the fetus, I think where this was coming from is from vaccines indicated for maternal immunization where you really want an antibody transfer to the baby to protect it from neonatal disease.

And I think the ability to also demonstrate antibody transfer then in an animal model from the dam to the fetus was really like a proof of concept issue, to say that you can demonstrate that you are able to show this; you know,

keeping in mind, of course, the limitation of an animal model.

But Carlo, don't you face the same problem if you develop a vaccine candidate, some preventive vaccine that you give to a non-pregnant population, and you do your proof of concept study in an animal model to see that your candidate is immunogenic and has the desired effect? And I think that's sort of why we wrote it that way.

PARTICIPANT [In Audience]: Right. I do understand the question if it is an efficacy question. I don't understand the question if it is a safety question. So I understand why you put it, because you want to make sure the intent is to have an antibody in the serum of the fetus. So it makes perfect sense in that case to go and test it, because that's in the intent.

But if you're just fishing for toxicity, it doesn't make any sense to me to go and look in the fetus, because I'm not sure the data are relevant. But I understand your point.

DR. VAN DER LAAN: Yes, I can agree. I have the same feeling in asking for the toxicological elements of this. First, as this so, what Dr. Barrow said, the exposure? And

exposure can be different from different vaccines. And the second point is then what Marion now indicated, that the exposure might have also effects that you want, intended effects in the neonate.

Other question?

MS. SAEGER [In Audience]: Polly Saeger, from NIAID/NIH. Maybe I've missed something here today. And it's entirely possible I did. But I'm thinking about, you know, we're in the government; we're helping various sponsors develop vaccines. And I'm right now responsible for setting up some of the resources to help with development of biodefense vaccines.

So I'm thinking, we're setting up these assays that would be required before we would go into phase III trials and whatever. In my experience, before when we were setting up assays, we've gone through a phase of trying to validate our assay, or at least make sure it's standardized. And part of that includes looking at negative controls and positive controls.

And what I haven't heard here, I don't think, is what I could use with working with my investigators and contractors in setting up these assays as a positive

control that would be appropriate for testing vaccines. I mean, did I miss something, or is there a vaccine or a vaccination schedule that can be used as a positive control in this kind of repro-tox assay?

DR. VAN DER LAAN: Your question is a double question. Referring to the use of a positive control and for the positive control standard, for that positive control I think every vaccine has its own schedule. But for that vaccine you have a standard--

MS. SAEGER [In Audience]: No, no. No, I'm not talking about--When you're setting up an assay, okay? So if someone has not been doing this before, necessarily, or I'm hiring a contractor to do repro-tox testing on an anthrax vaccine, okay? If it were a drug, I would ask them to show me data that they have been able to show a positive effect from some standard, known drug that causes the developmental toxic effect in this assay, so that I know their assay works. Because you have to be able to show an effect in a study.

Ken, do you know what I'm talking about? So for the vaccine studies, what would you recommend as a positive control to be used in the assay?

DR. HASTINGS: Well, in a standard repro-tox study for drugs, you don't use a positive control.

MS. SAEGER [In Audience]: You don't. But before I would hire someone to do that, I would want them to show me data that in their hands they can get a positive result.

Correct?

DR. HASTINGS: Right.

MS. SAEGER [In Audience]: So if you received data from someone you'd never looked at data from before, you would want to see that. So I mean, if you want to set this up and do it, what can we use? Other than rubella, are there any others?

DR. VAN DER LAAN: As far as I know, your question is a validation of the model.

MS. SAEGER [In Audience]: Exactly.

DR. VAN DER LAAN: And I think there are more people in the audience that are asking for that. I think that in all the discussions that we've had on the relevance of the animal models, that that's a very difficult issue. If you have to sponsor some researchers, I think then you have to keep in mind that such a particular safety study should be done under GLP. And so you should go to a company that is able

to do a GLP and has control data and so on, and is doing the right job. That's my interpretation.

MS. SAEGER [In Audience]: I understand all of that.

DR. VAN DER LAAN: Yes.

MS. SAEGER [In Audience]: The question is, other than rubella, is there any evidence that any other vaccine tested in this kind of system has caused a positive effect in the kinds of developmental tox studies we have seen here?

I believe Dr. Christian showed one that you said was related to the adjuvant.

DR. CHRISTIAN: Yes.

MS. SAEGER [In Audience]: And what I'm asking is, of all the other studies that people know about that have been done, can anyone give me--I don't want the details, but tell me, have there been ones that are positive, weakly positive, strongly positive?

DR. CHRISTIAN: Not that we've done. And we've probably done the most, so I guess you can't even use us. But I would say that what you want to look for, if we're going to restrict it to the usual developmental tox end points, you want to know that the lab historically has experience

conducting that; that they've worked with the species and can observe those end points in that species which is responsive to your vaccine; and that they may have other compounds that show similar things.

I was just thinking, for example, if we're looking for immune response, you might even look at something like, do you have evidence of uncoupling agents, for example, which cause fevers in animals. I could show you that and say, "Well, this is one potential thing that could happen as the result of the vaccine, and here is an effect of having a fever."

But it would be very difficult, since we don't have a vaccine, a therapeutic vaccine, that in my experience--and I don't know, maybe Paul has one, or one of the companies has one--that has had an adverse effect. It would be awfully difficult to do that as a positive control. To the best of my knowledge, there isn't one.

And the same applies to drugs, though. Because having a positive control drug merely identifies that you can identify some end points that change. It doesn't necessarily mean anything at all relevant to the new drug entity.

MS. SAEGER [In Audience]: Precisely.

DR. VERDIER: Just to answer indirectly to your question, I think we have some data regarding administration of cytokines in animals.

So Paul, I don't know if you want to comment. But it's not directly a vaccine, but you can imagine that your live virus will trigger a cytokine release. And we know that cytokines in mice, and also in humans, can trigger abortion. So it's indirect proof.

MS. SAEGER [In Audience]: Okay. But what I'd like to suggest, then, is that maybe FDA in their guidance set this up to take a look again at this after some period of time, that if we're doing--everybody, all the sponsors, are doing these repro-tox studies--that after a period of three to five years, or "X"-number of vaccines in specific categories have been looked at, that the FDA reevaluate whether or not to continue to require the studies.

Because I could see that for some categories of vaccines it could be a real issue. For other categories of vaccines you may find that there is no evidence after "X"-number of vaccines through that you've ever seen anything; in which case I would think you might want to reconsider it as an

absolute requirement, and do it only as a case-by-case basis.

DR. GRUBER: Yes. But now you raise two entirely different points. But I think we all agree with your last statement made, that with experience comes wisdom, and at that point we can reevaluate our approaches. And I think FDA has been doing this all along. But your point is well taken.

DR. BARROW: I'd just like to add one point. Why are you considering vaccines to be different to any other therapeutic class? Would you, for instance, say when you want to place a study to test an antibiotic, would you say, "I want to see positive studies with another antibiotic" before going ahead?

MS. SAEGER [In Audience]: Personally, if I'm going to spend money on a study, I want to know that the person, the group, that's doing the study has positive results. I think we know for many of the drug classes, if not all of the drug classes, or a whole bunch of them. I mean, the reason you do repro-tox is because things have come up positive.

Now, whether or not that totally correlates with what you see in humans is a different story. But at least you know

you have an assay that can give you a signal. And so far, in these vaccines, other than rubella--I mean, I guess it's going to take developing a database to see if this kind of study gives a signal.

MS. BENNETT [In Audience]: I actually want to make a comment about that lady's comment. Sorry, I'm Jillian Bennett, from Australia.

I was a little bit surprised. Because what we're doing in our conventional toxicology studies that we spoke about yesterday is, we're not actually trying to target a maximum lethal dose, or anything like that, because we've recognized that they're vaccines, and we're not trying to induce intentionally a toxic effect. So we put in a dose that we think gives us a margin of safety. And in terms of repro-tox, I actually took it from the same sort of perspective.

In terms of the guidance, I think that I actually have to say, in terms of mapping out our product development program, I found it really helpful to have something additional to the ICH guidance. Because it gives us some perspective to think about with respect to vaccines.

It probably would be helpful if we separated out those vaccines that were intended for women to be vaccinated during pregnancy, versus those who may be unintentionally vaccinated. And I think that would actually bring some clarity then to sponsors, in terms of their understanding of what's required.

I think the other thing is that, in terms of the category of the vaccine, probably vaccines that are recombinant, sub-unit vaccines, adjuvanted with something like alum, you know, people are probably--We have a long history of use of alum but, you know, there is some speculation about the safety of that. But they are antigens that are naturally expressed during infection.

And so I think the epidemiology and understanding of the disease and the sequelae of having the disease are also very useful in terms of what we may want to incorporate. But again, I think that's probably defined quite well in the guideline.

I think from my own company's perspective, where we have a novel adjuvant and it is something that we don't have a lot of experience with, I think it would be immoral if we actually didn't make some sort of attempt to understand the

developmental toxicity of that. And perhaps, if we do give a rabbit a 15-fold-high human dose, it might actually also be useful to give the equivalent human dose on a milligram-per-kilogram basis, just to give us an understanding of what the background level is versus an extreme level. Because in our normal animal models where we set our dosing, we've probably given them--you know, almost tried to mimic what a human dose would be. Thank you.

DR. VAN DER LAAN: Okay. Thank you.

I think, the last question.

PARTICIPANT [In Audience]: Okay.

DR. VAN DER LAAN: It's five o'clock.

PARTICIPANT [In Audience]: Oh, okay, very quickly then. We've been speaking a lot about IgG and trans-placental transfer. And when we address, though, working with live virus, that then becomes the concern about the transfer of the virus, in fact, across the placenta. And there are very rare reports of human neonates and IgM. And therefore, the conclusion being that the human neonate probably did see the virus as the result of immunization of the mother with a live virus.

Not being an immunologist, please deal with my technical question here. Would it be technically feasible to think, okay, allow the pregnancy of the dam to go forward and either the pups or the kits, whichever species you're using--Would it be feasible then to measure, given the differences in the immune response? This is my question, though. Could we have a surrogate marker, such as the rare report, as we see, of IgM in human neonate? Is that just not really possible?

DR. VAN DER LAAN: Are there technical persons in the audience who can answer this question?

[No Response.]

DR. VAN DER LAAN: On the panel? No. We have to think about it.

[Simultaneous Discussion.]

DR. VAN DER LAAN: We don't know.

MS. HOLME [In Audience]: Risa Holme [ph], from GlaxoSmithKline.

We have had a live viral vaccine where we've evaluated the ability of the virus to cross the placenta. And we evaluated the sort of standard repro development end points. And since we did PCR on a significant number of

pups and we didn't see any developmental tox, we felt that it was adequate to stop there. So we have had experience of actually doing PCR in mice studies following a live viral vaccine.

DR. VAN DER LAAN: Okay. Thanks.

Thanks for the audience for this discussion in this last hour.

I guess, to Marion or Mercedes.

DR. SERABIAN: I'd like to thank everyone for coming and staying. I'm not sure, per se, consensus was reached today on certain items; but certainly, some stimulating conversation, and a lot of issues for us to take back and think about.

Do you want to add anything?

DR. GRUBER: I thank everybody for coming to this workshop and participating in the discussion. That was very helpful. And thank you very much again. 'Bye.

[Whereupon, the workshop was adjourned.]

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