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ADVANCING SCIENTIFIC AND REGULATORY APPROACHES FOR USE AND DEVELOPMENT OF BIOMARKERS FOR PREVENTATIVE VACCINES MEETING

TUESDAY, SEPTEMBER 17, 2019

8:34 A.M.

5601 FISHERS LANE

ROOM 1D13

ROCKVILLE, MARYLAND 20852

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SCIENTIFIC MEETING

TUESDAY, SEPTEMBER 17, 2019

9:03 A.M.

DR. BROWNE: Good morning, everyone. So, this morning we're starting with something a little bit different. I'm going to talk about biomarkers and today we're really focusing more on practical considerations around biomarker development. But to start off, oh, excuse me, let's see, we are doing a survey and we really hope that you will take some time to think about this and fill it out. It's intentionally low tech. We have a paper survey that we're going to be handing out and it's really because, I don't know if you're anything like me, whenever I see a blank field, I'm perfectly happy to check one through five from very dissatisfied to fully satisfied, but when I have to fill in the little free text, I just leave that blank. So, we're asking you to put paper to pen today and give us your feedback. The questions are intentionally open ended and we want you to reflect on what you heard yesterday and answer these questions. It's anonymous just because sometimes we don't all feel comfortable getting up to the microphone, but we still want to hear your voices and we also want your open and honest opinion without fear of retribution. So what our plan is to collect these at the end of this session ideally, but if you really want some time to mull it over before lunch, and we're going to go through those during lunchtime, we're going to give our stakeholders a heads up, so the stakeholders, I ask that you meet us in the speaker presentation room, which is just around the corner, down the hall on the right, and I think any one of the support staff around here or organizers can show you to that area, and we'll give you a heads up on any of the comments that we might be posing to you at the stakeholders' session. Because this is going to be sort of a limited timeframe to review these comments, we might not get through all of them, but we will do our best to capture sort of main themes and high level items that we think would be helpful to drive the discussion forward. And furthermore, we will be reviewing these in more detail afterwards, and as Marion mentioned, when we publish the proceedings, if there is stuff that comes out of these surveys, we might be able to even include it there. So this is how we do it...

SPEAKER: So you should mention...

DR. BROWNE: Oh yes, sorry. Yes.

SPEAKER: ...that there's two surveys out there.

DR. BROWNE: Right. Oh yes, good point. So, there is a survey on the chair. That is not the survey we're talking about. We hope you find these accommodations nice, but ours is about the biomarker workshop. And it's being handed out now with pens. There are bins to the left when you exit, and they're labeled by sort of discipline, and that's really for sorting purposes, but for the context of the questions, we also ask that you answer which, what type of institution you're affiliated with because I think it helps frame the subsequent answers. So that's why there's a little redundancy there. So anyway, with that, the way we usually do it for advisory committee meetings is we read the questions to you so that you can think about them, but then you have them written, too. So the first question as I mentioned is what is your primary affiliation, and you can see the different answers here. Feel free to say what other is if you're other. Questions two is rank the top three diseases and corresponding preventive vaccines and development for which more data or better validation of biomarkers would have the greatest impact. This could include diseases not discussed at this meeting and those for which one or more vaccines are already licensed. Question three is are there cases where in your opinion use of biomarkers and/or focus on biomarkers has hindered vaccine development, looking forward, are there scenarios where you think the use or focus on biomarkers could be counterproductive or would otherwise be inadvisable. And lastly, if you were an advisor to the stakeholders listed below, what changes if any would you recommend they take and/or what do you view as the biggest missed opportunity with respect to development and use of biomarkers. So this may actually be one of the places where we can imagine the stakeholder conversation could get lively. Anyway, this is the process. You fill out your surveys. I mentioned the receptacles on the left as you exit. We're going to review these for common themes at lunch, and then we'll pose these questions to the stakeholders. So time for the old school survey.

(WHEREUPON, time was allowed for filling out the survey mentioned.)

DR. BROWNE: I understand there are three people in the overflow room. If you want to join us, there are plenty of seats in the main conference room.

(WHEREUPON, more time was allowed for filling out the survey.)

DR. BROWNE: Okay, maybe I will get started. There is still time during the break to complete the survey. We have a twenty-minute break after Sean's talk. So today I'm going to talk about use of Drug Development Tools Biomarker Qualification Program to advance development and licensure of vaccines. The goals of my talk will be to describe the FDA Drug Development Tools Biomarker Qualification Program, briefly go over the purpose of it, the taxonomy, overview of the process, and then I've included some links to resources that might be helpful. So there are three main Drug Development Tools programs at the FDA. There's clinical outcomes assessments, qualification program, animal models which is really directed at developing qualified animal models for use in animal rule approvals, and lastly the Biomarker Qualification Program. Drug Development Tools are methods, materials, or measures that aid in drug development, and it's important to emphasize that this process is optional. So this is not something that some new program that we're requiring developers go through to get a tool validated before they can move forward with their program. Today I'm talking about the biomarker program among these three. So we've heard a lot of talks about all the different ways that biomarkers can be used in vaccine development. This ranges from defining the patient population and conducting safety assessments, down selection of candidate vaccines, selection of doses and regimens contributing, and then, you know, as we sort of move forward in development, contributing to case definitions for clinical endpoints and establishing markers of protection. We have our own framework for how we think about biomarkers. Clearly, biomarkers are used in many different areas by clinical and basic science research communities, and there is some overlap, but fundamentally regulatory acceptance focuses on the data that support a specific Context of Use. So we heard that from Jeff Roberts yesterday, that the critical aspect of this is not so much around to how we define correlative protection

and so on and so forth, but really what is the context that we're using this biomarker, what is the decision we're trying to make. And around that, the considerations include the reproducibility of the data, the adequacy of the assays, and how the biomarker will be used in a development program. There are really two main ways in which biomarkers have developed from a regulatory perspective, and I think the sort of classic way that we think of as acceptance through an IND and an NDA, or an NDA and BLA submissions. But I want to kind of compare and contrast these two processes, both the drug development pathway itself and then also how the tools, the DDT Biomarker Qualification Program works. So you can see that in terms of the development objective, for an IND or licensure, it's really a single development program, whereas for a biomarker qualification, once a biomarker is qualified, it could be applied to any development program that wants to use it in that Context of Use. Another main element of this is transparency. So within an IND or a BLA submission, it's proprietary, whereas the Biomarker Qualification Program is intended to be fully transparent, again so that anyone who wants to use this tool has access to it. The responsible parties are different in that it's really the individual sponsor and the review division that are having communications around how this, the biomarker will be used in an individual development program, but in the qualification, it's typically, it can be anyone, so it could be an individual or a group, but generally it's consortia and then they interact with a specific group which is the biomarker qualification team, which is through the Biomarker Qualification Program in FDA, and it's populated by subject matter experts who can speak to that biomarker and how it will be used for regulatory decisions. The process is a little different. They're both iterative, but really in an IND, the biomarker gets developed through interactions along the development pathway. Whereas the BQ process through 21st Century Cures and PDUFA VI has been formalized, and there's a formal process which I'll go through later. The risk is different, too, because the risk around a biomarker in an IND is really the sponsor who is developing their product, but in the context of a BQ program, it's shared among the consortia. Biomarker information is provided in drug labels and review memos in the classic IND and BLA or NDA, and then in terms of BQ, it's posted on the website, all of the data to

support that qualification and the thinking from the FDA is publicly available. And then again, as I've already said, in an IND, it's the sponsor who uses that biomarker, whereas with a BQ, with a qualified biomarker, anyone can use it. So I mentioned 21st Century Cures and PDUFA VI, and what they mandated is to establish a taxonomy for biomarkers for use in drug development through a public process, and to formalize a three-step submission, to formalize that process, it required transparency and specific timeframes for review and also to have public meetings and guidance developed to help developers understand what we're trying to do. So today I'm really going to focus on the taxonomy and the process. So Jeff mentioned earlier the best group, which is an NIH and FDA collaboration to develop this terminology, and you can see I have the link to this information. It's a glossary of terminology for different uses of biomarkers and how they could be applied to product development and clinical care. It was created by this working group and it's just intended to have a standard language. It's a living document so that as our understanding of how biomarkers are going to be applied changes, we can introduce new terminology or modified terminology accordingly. So just to try to define biomarker from this perspective, it's a defined characteristic that's measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention including therapeutic interventions. These can be molecular, histologic, as we heard with, you know, CIN in the setting of HPV vaccine, radiographic such as tumor size, physiologic characteristics are also types. But importantly, a biomarker is not an assessment of how an individual feels, functions, or survives. That would fall under the other category of a clinical outcome assessment. So there are a number of categories of biomarkers. I want to just mention that they are not mutually exclusive, so a biomarker can fit into many categories and this is not an exhaustive list. And again, this list could expand as our understanding of biomarkers expands. But some examples are a susceptibility or risk biomarker, which might be in the case of vaccine development, prevaccination serostatus, so that you know your patients are at risk, or subjects are at risk of the disease that you're trying to prevent, a diagnostic biomarker which could be say serum PCR for a laboratory-confirmed infection as a clinical endpoint, and then

there's a monitoring biomarker. We're going to hear from Dr. Sean Murphy talking about his experience on the other side around the Plasmodium falciparum biomarker qualification, which was the first qualified biomarker for vaccines at FDA. But his biomarker could theoretically also be a diagnostic biomarker, so I think it just underscores that these are not necessarily mutually exclusive categories. You know, we heard about safety biomarkers yesterday such as fever or lab tests, and then there can be a response biomarker which, you know, ultimately would be an immune marker of protection. I mentioned prognostic biomarkers and predictive biomarkers because those are other terms that we use, but as you can see, I was having trouble coming up with examples that applied to vaccines to prevent infectious diseases. So our definition of qualification is determination that a Drug Development Tool, when used according to its proposed Context of Use, and we often refer to that as the COU, can be relied upon to have a specific interpretation and application in drug development and regulatory review. Qualification may be rescinded or modified based on a determination which may include new information that calls into question basis for qualification. So this is legislation from 21st Century Cures, and, you know, I think the fact that we're saying rescinded or modified doesn't necessarily put the most positive spin on going through this process, but I think a modification can also be expanding your Context of Use to having increasingly more impact on drug development. So the Context of Use is a statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development related purpose of the use. So generally there's a format that we apply which starts with the best glossary category, the type of biomarker it is from that list I showed you, and I'm just giving you an example here that we'll hear about shortly, so in this case it was the monitoring biomarker, and the purpose in drug development was to inform initiation of treatment with antimalarial drug, and the stage of development is early stage, which would be proof of context studies in the setting of controlled human malaria infection, and the target population in this case is healthy subjects. In terms of the process, it's really a three-step formalized process. There's the letter of intent. So that's when the requester submits their letter, the biomarker review team is, well, the letter of intent

is reviewed and it's accepted to the program, and I'll sort of get into some of those criteria in the next slide. A review team is assembled and the briefing document specifications are sent to the submitter, so this is kind of an initial list of questions. Then the qualification plan is the next step, and that's really the meat of this process. In some ways I almost think of this as sort of the IND phase for the biomarker. The briefing document is reviewed. There's an internal meeting. There are pre-meeting comments sent. There's a face-to-face meeting with the submitter. But this can be iterative with a lot of back and forth of questions and answers and additional studies and data that might be required to support the proposed Context of Use. And then once the full qualification package is submitted, that's kind of like submitting a BLA I would say. You could almost say that the Context of Use is a little like the indication statement where the data support the proposed Context of Use, just like the data in a BLA support indication statement. And the full qualification package is received, but at this point there shouldn't be too many surprises because we've gone through this qualification plan. And it's reviewed by the team. Additional information may be requested as needed, but at that point, a regulatory decision could be made, and I think that one of the important and nice aspects of this is that once this biomarker is qualified, it is recognized across the agency. So sometimes we'll have folks from CDER and CBER, for example, on the Plasmodium falciparum qualification group. There were representatives from both groups because the biomarker could be used in drug development pathways as well as in vaccine development. So acceptance of the biomarker into the qualification program, and this decision really lies in sort of the strength of the argument made and the letter of intent, and it needs to address an important development need. There needs to be sufficient information submitted so that we think there's a high likelihood of success and the feasibility of the approach needs to seem reasonable so that we're, you know, all spending our time well. Again, this is language from 21st Century Cures to say the prioritization of review of submissions is based on the severity, rarity, or prevalence of the disease or condition targeted by the drug development tool and the availability of lack of alternative treatments for such disease or condition, and the determination that such Drug Development Tool and proposed COU

is a public health priority. So I think in vaccine development and facing, you know, new emerging infectious diseases and, you know, difficult clinical trial designs, as we heard over the course of yesterday, really is why I'm up here because I think that in terms of a lot of the consortia that are working together to advance vaccine development, this could be a very powerful tool. And then, you know, I just want to underscore that qualifying a biomarker for something to support early phase development, while it doesn't necessarily seem as robust as say having a biomarker for a clinical endpoint, the Context of Use can be expanded as data are accrued. So this is the regulatory, this is the framework that was developed and is kind of the schema of how we view biomarker qualification in the context of drug development. So there's the needs statement, which would be the letter of intent, and the Context of Use, which defines the class of the biomarker and what question the biomarker is addressing. And then that's really intended to address, to impact the patient and the way we view decisions made, regulatory decisions made around patients and public health is through this Risk-Benefit Assessment. So in the context of biomarkers, it's really about what the biomarker is going to contribute to drug development. And so examples could be improved sensitivity, improved selectivity, providing a mechanistic context, or a clinical endpoint that would help approve a needed vaccine. I think the risk, the further you get from a clinical endpoint, the more risk there is that the endpoint does not truly reflect the effectiveness of the product, and so that risk has to be calculated in the context of what the benefit is and what is the vaccine that you're trying to develop. And that risk-benefit calculation really informs the stringency of the data on the evidentiary criteria that would support qualification of the biomarker. So those data need to characterize the relationship between the biomarker and the clinical outcome, the biological rationale. Ideally, they're independent data sets that all support the same conclusion. There should be a comparison to the current standard and then an analysis of assay performance and statistical methods. And again, if you're qualifying a biomarker for early phase development, that's very different than qualifying a biomarker where you're going to make a regulatory decision on a vaccine that's going to be introduced into the entire healthy birth cohort. So that sort of gets at the risk of qualifying a

vaccine in early phase development versus later. So other considerations for a qualified biomarker, I think I've already said this, it's recognized across the agency. It still is at the discretion of the product review division to determine the appropriateness of this biomarker, but you know, I think ideally if it is truly being used in the Context of Use for which it's qualified and there are no major issues with study design or study design flaws, that it will generally be accepted without additional data needing to be supported to submit it to support the use of that biomarker. And there still is potential to use that biomarker outside the proposed Context of Use, and that would just be a discussion with the review team if they deemed it acceptable in that context. So here are some links to resources. We have a common portal where we accept submissions now. There's the CBER Qualification Program, contact info is here. And then I just wanted to mention that the 2017 draft guidance for formal PDUFA meetings specifies that you can request a type C meeting to receive early consultation on the use of a biomarker as a new surrogate endpoint that has never been previously used. So that's another mechanism for communication around development of biomarkers. I have the link here to the best definitions and the NIH biomarker information and resources page because they've been very engaged in advancing our thinking on biomarkers. And then Chris Leptak, who runs the Drug Development Tools program at CDER, has a nice paper and sides translational medicine kind of outlining some of the thinking around this program. So summary, biomarkers we know have a long history of use in medical and scientific communities and for regulatory purposes. Recent legislation provides additional avenues for use of biomarkers for regulatory decision making, and biomarker qualification is an optional program intended to facilitate development of biomarkers for regulatory use. It's formalized. It's intended to be collaborative and transparent, and qualified biomarkers are recognized agency wide for the intended Context of Use. I want to acknowledge a number of my colleagues, Marion, Jeff, and Valerie, who were the FDA team with me, as well, organizing this conference with our co-organizers at NIH and CEPI, and then some of the other folks who have also participated in helping me with my

slides. And with that, I guess I will invite Sean Murphy up to talk about his experience going through the Biomarker Qualification Program.

DR. MURPHY: Thank you very much. Thank you for the invitation. I do need someone to change the slides, though. So while they bring up the slides, I just want to say a couple of things that, thoughts that came to mind watching Sarah talk, and the first of which is when we entered this program, it was housed at CDER, and during the time that we went through the program, the 21st Century Cures Act came into being, and one of the benefits to us is this agency-wide recognition of the biomarker, which for the malaria field carries a lot of weight. We started advocating that this would be certainly applicable for drugs and we hoped for vaccines, and it turns out that that is indeed the case. So I am at the University of Washington. My lab, we do vaccines and diagnostics. We are very interested in biomarkers that explain how malaria vaccines work, but today I'm going to talk about this diagnostic, or monitoring biomarker if you will, that tells us when participants in human challenge trials when the vaccine is not working. I have a few disclosures, none of which pertain to the content of today's talk, and this is the basic outline. I'm going to briefly tell you about our biomarker, how we test for it, and then spend most of my time talking about our experience in the program and some lessons learned that I think, I hope will be applicable to people outside of the malaria field, as well. I don't need to rehash the program because you just heard from Sarah here, but I would say that Chris Leptak's paper that's cited here and was cited in Sarah's talk is a very good resource for explaining to amongst other people funders and other groups who really don't understand what we're doing in the biomarker qualification process. It's very confusing to academics and funders and everybody when you say validation, that means different things, and this is a very useful document to help guide you and convince people that this is an important process. So our goal in our malaria program was to go forward as an emissary to the, for the malaria field to FDA to achieve regulatory acceptance of this monitoring biomarker so that we could use it as a safety or efficacy endpoint in vaccine and drug trials. And we hope that this would do a number of things. We hope that this would encourage harmonization of assays. There have been dozens of

different malaria PCR and RT-PCR assays published, that this would encourage harmonization of trial designs, how people use this when they treat on the basis of this. It would improve testing quality and improve the quantitative data that was coming out of these trials. If you use blood smears, for instance, for malaria trials, you very much get a black and white picture of negative, negative, negative, positive, treat the patient, negative, negative. If you use a molecular endpoint, which I'll show you the graphics of, we'll show you the rise and fall of parasitemia, you'll see a much more nuanced picture about how the vaccine is working or whether there's partial protection and what have you. So we have a lot of difficulties in malaria. We have fifty-three hundred genes in our parasite, but one of the very enviable things in the malaria field is that we have a very crisp human challenge model that's very safe, has been around for a long time, and allows us to quickly evaluate whether drugs or vaccines that are coming down the pipeline are working. And this controlled human malaria infection model basically follows the graphic that's shown here. We have to, up until recently we have had to use mosquitos as little flying syringes to deliver the vaccine, and so upstream of human challenge studies, you have to culture the parasite, infect the mosquitos, and time the infection just right. So the choreography of these studies historically has been very complicated. It's been made easier by injectable forms of the sporozoite that are in the mosquito salivary glands. What happens when these people come in for the day of challenge, which is listed here as day zero, they're bitten by mosquitos or injected with parasites, and preceding this, they've been vaccinated or they've received a prophylactic drug or in some cases they are about to receive a prophylactic drug. And the parasite will then go to their liver for about six-and-a-half days where there will be no clinical signs and symptoms. And on about six-and-a-half, seven days in an unprotected person, the parasites will emerge from the blood, except thick blood smears, which is a hundred-year-old test that has been used forever, will probably not pick up the parasites that day. In fact, it won't really pick up the parasites till several days later, about the time that people sometimes have pretty significant symptoms, at least in a healthy subject study. So it's certainly not an unsafe way to do these studies, but what we have recognized is that molecular diagnostics can help us identify the

infection basically as soon as the parasites are fleshed out of the liver. And in Seattle where we don't have endemic malaria, if you have any molecular signal or microscopically positive parasitemia and the vaccine or drug was intended to prevent that, then it's a pretty clear sign to us that the vaccine or drug didn't do what it was intended to do. So this isn't new information. We have known for a long time that we can use molecular diagnostics to accelerate infection detection in malaria, and this graphic shows that that infection detection is accelerated by something like two to five days. The black and black dotted line shows our RT-PCR assay in comparison to thick blood smears from a compilation of studies that we have done in Seattle, and what you can see is that there's this accelerated infection, infection detection, rather. So what is it exactly that we're detecting? Well, you don't detect the parasite in the liver. You detect the parasite when it comes out of the liver, and in the case of P. falciparum, which is the major species we're working on, the parasite looks like this. Where the green text is, these are the parasites that can be found in peripheral blood. But on the red text side, these are the more mature parasites, the schizonts and trophozoite stage parasites that have a property of adhering to endothelia to avoid removal in the spleen. And so all we see in the blood are these ring stage parasites. Well, for us this is very convenient because each ring stage parasite has one quanta of parasite DNA and RNA, and we target the 18S ribosomal RNA, which is encoded by a couple different genes that are expressed either asexually or sexually and so they've been given terms A and S. Well, in this ring stage, the parasite expresses thousands of copies of 18S ribosomal RNA, so the parasite does the first step of really improving the sensitivity of our test if we use a reverse transcription based test. And so when we do that, when we do reverse transcription PCR compared to regular old PCR, we can detect a single parasite in a 50 microliter whole blood sample, and with that we feel that we can really detect parasites on the first day that they emerge from the liver. So the assay that we use is an RT-PCR assay reverse transcription PCR assay, and you know, very simply our input is whole blood and several hours later our output is copies per mL of pan-Plasmodium target, a P. falciparum target, and an endogenous internal control. And then for P. falciparum, we take the extra step of trying to interpret that copies per mL into

parasites per mL, which is the language that malariologists have spoken for a long time. We're not the only people, as I've alluded to, who have known that diagnostic, molecular diagnostic tests will accelerate infection detection, and to prove that point, one of the pieces of data we submitted in our qualification program was this review of all of these different cohorts, some done by us, many, most done by other groups using a variety of 18S ribosomal RNA or ribosomal DNA assays that show in the squares the time it took on average to detect the parasite's bimolecular methods in that cohort and in the circle the time it took to detect them by blood smears. And you can see in every case, molecular detection is earlier, in some cases much earlier than blood smear detection. So why would we want to do this? Blood smears are perfectly adequate as a safe endpoint for human challenge studies, and this is the normal course of what would happen in a blood-smear based human challenge study. We don't have, the quantitative data here is just modeled off of a molecular quantitative assay, but at the point where the arrow says treatment, this is where someone in this study would have become blood smear positive, they'd be treated, and the parasites would quickly be eradicated from their body. But if we use a biomarker-based definition and use that to treat the person, we can turn the corner earlier and still get the same answer about whether the vaccine or drug worked. And with this, we have fewer adverse events. We've managed to eliminate the so-called hotel phase from our clinical trials. So we used to house people in a hotel during the window in which they might become symptomatic from malaria, and so that added cost, and the first few days sounded like fun and then afterwards, you know, two weeks in a hotel is no fun for anyone. So we have happier trial participants who go home and they tell their friends to be in our studies and we then are able to continue to recruit people. And importantly, we still get the same quantitative data that allows us to do things like model how many parasites survived in the liver and things like that. So with this experience, we went to the FDA and we submitted a letter of intent at the time. The steps through the program were different than they are now, pretty similar but a little bit different, and in essence, our qualification package consists of two parts. One is the analytical validation of the assay we use for the biomarker, so does the test tell you what the test says it's going to

test for, and with a validated assay then, we clinically validated the biomarker, which is basically does it always agree with blood smears, does it accelerate infection detection, what is the rate of false positives or false negatives in these studies. And this was a big undertaking for an academic institution to do, so I always like to tell people we filed fifty-eight appendices and, you know, some of the stats on here because it was a major undertaking. And you know, when we try to publish these kind of things in journals, I would say that sometimes journal editors view these things as boring, but at the very least, this is boring but important, and really what it is is if you can't measure how your vaccine or drug is working, then kind of why do the study at all. So I think that this is very important and fortunately we've managed to convince the malaria field of the same. I just want to show you a couple snippets of data from the qualification package. So this is a way to view the PCR data using different thresholds. So we can treat people at the first sign of smoke, like as soon as our very sensitive PCR, RT-PCR assay goes positive, we could treat people. And if we did that, that would occur, you know, on average at least two, little bit more than two days before any symptoms. It's even greater difference if you look at like grade II symptoms, and then if you were to ratchet up that threshold, let's say three to twenty parasites per mL or a molecularly defined 250 parasites per mL, well eventually you would regress to being no different than thick blood smears. So if you view the molecular data with these different bins or different thresholds, you can kind of see, if I was going to design the study and I wanted to treat early or I wanted to let the parasitemia go a little to see what happens, how might I expect to derive the improved adverse event profile. We also shared with FDA our view on how molecular diagnostics help you understand partially protective malaria vaccines. It's easy to understand completely protective vaccines. We basically found that there should be no blood smear positivity, and correspondingly, there should be no molecular diagnostic positivity, and indeed that's the case in people who are protected. In people who are, the basically naïve placebo controls, the parasites emerge almost immediately from their liver on day seven and we can detect it right away. But what about those people who have blood smear positivity that takes a little bit longer to occur? What we find is that the biomarker, because it's so

sensitive, it detects parasites coming out of the liver, most of the time right around day seven or eight. But a good way to delineate partial protection isn't so much any qualitative positivity with a biomarker, but what, how many parasites were there. And so you can delineate these different groups, that is people who became blood smear positive on day seven, eight, nine, or ten or eleven, or you know, thirteen, fourteen, and they will have different times that in this case takes them to reach an estimated density of 250 parasites per mL. So you could pick a different threshold. Then you have to balance the adverse event profile against kind of what data you're trying to get for partially protective vaccines. We're not trying to make a partially protective vaccine, but in the event that that's what comes out, you can derive extra info from what might be a disappointing vaccine trial. So in October of last year, the FDA issued their agency-wide qualification for our biomarker, and the qualified Context of Use Sarah already shared with you. This is a monitoring biomarker and in that, it means we use it to initiate treatment because these people who are in non-endemic settings shouldn't have malaria. We need to treat them so we can safely send them on their way. At the moment, this is for healthy subjects in our controlled human malaria infection studies, predominantly in studies that would be done in the U.S. or Europe. So I thought I would share with you a variety of lessons learned in this process, and the first is that the FDA was very good at helping us narrow our scope of what we wanted to review with them. So I am very ambitious. I was like oh, let's, here's all the things we want to use it for and let's just do it. And they, so some of these are listed here. This is, really represents what we see as our program going forward, and so we were able to share this vision with the FDA and then we picked the most practical one to do first, which is this non-endemic controlled human malaria infection (CHMI) safety/monitoring endpoint. And that was really useful because the scope of the amount of data that we were going to have to present to FDA certainly as an academic investigator wasn't apparent to me at the outset but is now. During the qualification process, there were a variety of hot topics of discussion, collegial but, you know, things we kept coming back to, and so I listed them here. One of them that may face you is what do you do when your new test is a thousand times better than the gold standard that's been around for a

hundred years. And this is really the recurring theme of our biomarker project, which is how do we replace blood smears with molecular diagnostics. Well, if you look at the normal square of true positive, true negative, false positive, false negative, when our test is positive and blood smears are negative, you know, a simple view would be that we got it wrong, but we didn't and the way to show that is to get all your friends who also have good assays around the world to be willing to do testing in parallel at great cost to show that in fact the molecular target of your test is actually there every time and that's corroborated by different groups and different labs. So we did lots of discrepant analysis to prove that we were actually detecting the biomarker, and this was easier to prove perhaps in these studies because if a person was biomarker positive on day seven or eight but then they became blood smear positive on day eleven or twelve, it all fit with that person's trajectory. We had a lot of discussions about how restrictive the qualified Context of Use might be, and my colleagues in malaria wanted me to make sure that we didn't paint ourselves into a corner by having certain parts of the qualified Context of Use be too restrictive. I would say the FDA recognized that issue, and what I mean by that is if the FDA said when this is positive, you must treat at parasite density X, it would really mean that people who thought their trial needed a slightly different design would be restricted. And so our Context of Use actually doesn't specify how to treat. That would be enshrined in that group's IND after they say that they're going to use the biomarker, then they say, you know, what they will do in response to it to protect their participants. So I appreciated and I think it made sense to go that route. We also had discussions about, you know, what to do about copies per mL, which is very common in virology but is not the view of malariologists, and so we now report both, but copies per mL is the FDA's preference. And then I have safety versus monitoring listed here, as well. So we hope that we would, safety versus efficacy, rather. We hope that this could be viewed as a safety and efficacy endpoint by the Context of Use. The first one lists this as a monitoring endpoint. Now I think you will agree that if you were to treat at the very first sign of biomarker positivity and then all the parasites go away and that's the only indication of whether the vaccine or drug worked or not, you have used it as both a monitoring and an efficacy

endpoint. But sometimes we might not do that, and what we definitely will do is treat in response to it, and so we limited our scope to that at this stage. Again, how you use it would be enshrined in the IND for that biomarker, but some of these things which now seem very logical to me didn't seem logical to me at the outset. And so the process can be lengthy. We were the first biomarker to go through a process that involved CBER, CDER, and CDRH in the review team, and it took several years. We filed our letter of intent in December of 2014 and got the qualification letter issued in October of 2018. I'm not sure if this would go faster if you weren't trying to replace a really well-accepted gold standard, and I do know that the revisions in the 21st Century Cures Act are likely to accelerate this process. It was actually a very educational and collaborative experience. Our lab, our program, all of it is better for having learned from all of the experts on the team and to have done like a risk analysis and think about, you know, what are the holes in our assay and how do we use this. So that was very collaborative as the program is intended to be. And then lastly, this process, the qualification, can do what we hoped it to do, which is drive harmonization, lead other groups to use the biomarker. Some groups were already doing that. So under INDs, people have stopped using blood smears in certain trials even before this biomarker was qualified. But you had to prove it to the FDA every time you filed an IND, and now that is made easier. And so, you know, we hope that this will continue to be the case and that is we work to expand the Context of Use, it will become more applicable to other groups, as well. I just want to show you one bit of data before I close. All the data that we submitted to FDA was based on retrospective predictions of what would happen if we treated in response to biomarker positivity instead of blood smears. So we would say oh, if we treated here, we think we would spare all these adverse events. But we didn't really know if that would be the case until we did it with a primary endpoint. And so this is an example of one study that was published last year. This is a drug study where we were testing a prophylactic drug for malaria and we were able to, you know, use this repeatedly in many cohorts to show the difference between drug and placebo control. But what's important in terms of the benefit of using a biomarker is listed on the right. At the same time we did this study, an exact copy of one of the

cohorts was conducted in Germany by Benjamin Mordmueller, and the only difference these two studies was that they use blood smears and we used our molecular endpoint. And so in their study, they had sixty adverse events including several grade III fevers, and in our study, we had twenty-two malaria-related adverse events and no grade III events at all. So we think this is a nice example. It's a small study but a nice example of sparing symptoms by using this more sensitive endpoint. So in summary, this was the process we went through to obtain qualification of the biomarker here at the FDA. We work collaboratively with the group and we think that these molecular endpoints add a lot to the malaria field and intend to continue working on this process to expand the Context of Use to other places like endemic, malaria endemic parts of the world where obviously we have to do a lot of clinical trials, as well. So there are many people to thank. Many of them are co-authors on a paper that we published on this experience earlier this year, and in particular, I'd like to call out a couple of them who were very generous in providing access to clinical samples and clinical data sets, and in particular, that's Patrick Duffy and Sarah Healy at the NIH at the LMIV who provided material that was really indispensable to proving our case to the FDA. And then in addition, we've been funded to do this work by the Gates Foundation, who recognizes the utility of this to the field, and so we thank them and all the partners, as well. Thank you.

DR. BROWNE: I guess we have some time for questions, if there are any.

PUBLIC QUESTION: This is a very elegant study and really good example of qualification of the biomarker, but it seems to me that it really dependent on the fact that you knew exactly the day of exposure of infection. I don't fully understand how this can be used in the field. Most of the context of, we don't even necessarily know when we were bitten by the mosquito, and even in the context of preventive vaccine, when we look for breaks of infection, it's almost like how do you really know when to start testing for your RT-PCR so they could get the benefit, the added benefit of earlier diagnostic?

DR. MURPHY: So it's a very good question, and this is why we tackled non-endemic sites before we tackled endemic sites. You know, I think people think of like malaria infections in the field as a big iceberg where there's symptomatic people with higher parasitemia above the water line, and then all of these progressively asymptomatic and lower density infections. So what we don't know is how in those areas where you're testing vaccines, how things like pre-existing immunity are going to affect our ability to delineate between what was there and what, you know, was a new infection. This isn't an assay that would, for instance, delineate between the, you know, snips of a challenge strain compared to the things that are out there in the field. What we have seen when we've done testing for epidemiology studies and other studies done in Africa and parts of South America and Southeast Asia is, you know, we find lots of asymptomatic infections in epidemiology studies and we're not alone in that situation. I think much of it will depend on the context of use and the purported mechanism of how the vaccine you're testing is thought to work. So if what you're doing in the liver is really trying to create sterile immunity where parasites shouldn't be getting through, and if you prove that you've cleared that prior to vaccinating or prior to your window of monitoring to see if they've been re-infected, then this kind of testing would very sensitively pick up infections on the way up, on the way down, or of course at the peak. So, you know, we've looked at different study designs where people test weekly or people test monthly. It's expensive to test on a very frequent basis, and so, you know, your hands are tied somewhat in study design. The challenge studies are enviable, of course, for the reasons you say. So it will be very interesting to think about how to do those studies. I think we'll, you know, initially follow the way that RDT and blood-smear based study designs have been used, and this really will just allow us to see more deeply into the water in those cases.

PUBLIC QUESTION: Hi, good morning. I want to say something, former FDA. So this question is addressed to Dr. Browne. As we heard yesterday, in the field of vaccines, we've been using biomarkers from the very beginning and just talked, so right now the paradigm for advocating this BLA is to develop a biomarker in collaboration with the FDA and have agreement on

that biomarker for the Context of Use and eventually application. So, and this is done within the context of the IND process. Can you just sort of remind us what value added does this have for applicants to access this pathway that separate above or separate from the current paradigm where you're developing these biomarkers on a one-for-one with the agency? And if you could comment.

DR. BROWNE: Sure. I think the key is really around the transparency of this program because I think that often in the IND space, because of its proprietary nature, a lot of work goes into developing a biomarker that could potentially be utilized by another development program. So, you know, I can imagine in the private sector developing a biomarker that your competitor would then be able to apply in a narrow program. It might not be as palatable, but I think particularly in vaccine development and in resource limited situations, there could be a huge opportunity, I think both in the private and public sector, for not reduplicating efforts and for really developing these endpoints that then can be used across different programs, you know, in terms of sharing information and resources. And I think the key is in this program. All of the information is publicly available in terms of the assays that are used, all of the information that supports the qualification, and so that information can not only be used by another developer who wants to use that biomarker and potentially that assay in their own program, but it can also be a resource for somebody who wants to develop a biomarker for a different disease endpoint or a different type of, a different vaccine development program, just in terms of, you know, for example, some of the lessons learned that Dr. Murphy talked about might be applicable. And I guess, you know, the one thing I wanted to mention along those lines is that the biomarker itself is what we're qualifying, so the assays that are used to measure that biomarker are not what's being qualified in this case. It's really that endpoint in the proposed Context of Use.

PUBLIC QUESTION: Okay. And there was a follow-up question, too. So from a regulatory standpoint, if you were to have a qualified biomarker developed by, let's say a consortium, would that be in the form of a Master File where we could, the applicant, all applicants could simply

refer to it in the application process? Has, I don't know if that's been worked out but how do you do that?

DR. BROWNE: No, it's, I mean, it's a publicly available recognized, so for example the 18S RNA is listed on our externally facing website as a qualified biomarker along with a number of other biomarkers that have been qualified, largely in the drug development space because this is really this first vaccine applicable biomarker that we have, but you can go onto the, if you type in FDA biomarker qualification, you can find all sorts of information about the process and then a list of all the qualified biomarkers, what their Context of Use is, and then you basically say that I'm going to use this biomarker as this endpoint for the same Context of Use. Now potentially as Sean mentioned, you know, his study might also use that biomarker to look at exploratory efficacy endpoints to rule out vaccines that, you know, that he doesn't want to move forward with, but what we're recognizing it for is for a monitoring biomarker in that specific context. Is that helpful?

PUBLIC QUESTION: So it's become common to co-develop antibodies in, this is for segments, antibodies, and vaccines at the same time, for HIV, for Ebola, et cetera, and it's going to become more common as we go into the emerging infections. So my question, since antibody use with prophylaxis is regulated by CDER and vaccine use is regulated by CBER, how does the agency coordinate their activity so that the developers, who are often co-developing these things, and coordinate their own activities?

DR. BROWNE: So when a letter of intent comes in through the portal, it goes to leadership across the different centers because it is recognized across the agency, and it essentially gets evaluated for its potential to be used in the different centers. And if the different centers or offices can envision a place where this biomarker might be used, then they will put subject matter experts on the review committee to make a decision, and so I think that is the goal in my, you know, as an agency, we're all committed to cross communications because we recognize that once this biomarker is

qualified, we all have to generally accept it for that proposed Context of Use. So we have a real vested interest in making sure that the people are at the table evaluating the data.

PUBLIC QUESTION: So question for Dr. Murphy. So I was curious for the qualification, but I'm a little puzzled by a duration of four years it took to qualify this. So can you help disseminate it, so where you are at the beginning of the journey?

DR. MURPHY: Yes, so the, I think the, we probably, let's see, so the four-year duration I guess I would say is equally shared by the FDA and us, maybe two years of their review collectively between the letter of intent and the qualification plan and qualification package itself, and then probably two years of us accruing additional data from what was, there was two completed studies when we entered the program and one ongoing study. And honestly, the thing that took the longest for us on our side was obtaining like data transfer agreements and all the kind of paperwork stuff that makes it complicated to get data. The data analysis itself, you know, didn't take that long. So, and that's with really excellent collaborators. These processes take too long, I think we would all agree with that. And then on the FDA side, it's not as if we sent it off to FDA and then we didn't hear anything. We did have several like iterative back and forth processes, so we filed, after the qualification package went in, we filed two additional responses that added a whole lot of data to specific questions that they had. We had a face-to-face meeting, we had phone meetings, we had a discussion at the time that the qualification letter was to be disclosed. And during this process, so I think, the other thing I would say is that during this process, it went from pre-21st Century Cures to post, and the review team did not change but the leadership of the program at FDA changed, and so there was also some I'm sure paperwork on the FDA side trying to figure out, you know, how that was going to happen. So we appreciated that the review team didn't change and we didn't have to reeducate the group about what we were doing. But collectively, that took a while. My understanding is that it was actually much faster than the first drug biomarkers that were put forward and considerably faster, and so I think, I'm sure the FDA also hope that in the future it will accelerate even more than that.

PUBLIC QUESTION: Sure. If you don't mind, can I just ask a follow-up question? So obviously I understand this is something new. We are all learning from both sides, but just, maybe the second question is for Dr. Browne with the FDA, do you guys have any status on the median time, median duration that it took to qualify a biomarker?

DR. BROWNE: I don't off the top of my head and I'm not sure it would be useful because firstly, you know, 21st Century Cures was passed in December of 2016, and that mandated formalization of the BQ process and actually establishing timelines for review. So before that, you know, we had been working on qualification for ten years, but this was really a very rapidly evolving area of policy and learning experience for us. So what I can say is that moving forward, there is a legal mandate to establish those timelines, similar to say a BLA Review clock.

PUBLIC QUESTION: Thank you.

PUBLIC QUESTION: So I can make this very short. I had the very same question that was just asked, and I think you answered that. Thank you.

PUBLIC QUESTION: I was, this is to both of you, Jerry Skinner. Do either of you see qualification of an immunologic biomarker in the context of efficacy and licensure? For vaccines? In other words, you know, an immunologic boundary.

DR. BROWNE: Sure.

PUBLIC QUESTION: Is that, do you see that in the future? Is that a possibility?

DR. BROWNE: I mean, I think, you know, I think we should sit tight and wait to hear from the session five speakers because I think there's a lot of interest in that in developing endpoints, and I think qualification would be a great approach to establishing endpoints that we would recognize for clinical trials where clinical endpoint efficacy studies are infeasible. You know, the evidence to support the qualification will be substantial, so it will take work and I think that's where the consortia come into play.

PUBLIC QUESTION: Well, the vaccines, once a vaccine is licensed, it's very difficult to do another placebo controlled vaccine trial. Does that come into your considerations for not feasible? Because there's an ethical issue. If we've got something that works, it's hard to do a, you can do it and it has been done, but you know, giving placebos in the context of knowing that another vaccine works is difficult.

DR. BROWNE: I'm not sure that, you know, you could use those immunologic markers in say a comparative trial as well and look at immunologic noninferiority. I mean, I think that in some ways, we've been doing this for decades when we use, you know, tetanus antibody levels or hepatitis B, you know, for licensure of those vaccines, we're using antibody levels to make a regulatory decision for licensure. So that wouldn't change. I think, the point is is that happens within a development space and is submitted to a BLA, whereas in this case it's being widely recognized as an endpoint. Those are functionally qualified, if you will, because they're recognized by the scientific community as being a meaningful endpoint, but I think this moving forward will formalize the process earlier on for drug development purposes.

PUBLIC QUESTION: I see.

PUBLIC QUESTION: So I have one practical and one philosophical question. It's Julie Fletcher from NIH. So practically, if I were to submit an IND for malaria product and I reference your biomarker as my monitoring safety endpoint for trigger to treatment. What level of complexity or how onerous is it on me? What's the burden to me to prove how I will use it? Because it's not assay specific, right? So can you describe that quickly? And then I'll have...

DR. BROWNE: Sure. I mean, I think the standard for how you would validate your assay to demonstrate that you are measuring your biomarker accurately would be the same. And so that is really dependent on what phase and developments you're in.

PUBLIC QUESTION: Okay. So whether I reference that biomarker or not, I would present that?

DR. BROWNE: You would still need to show us that you can measure that biomarker appropriately.

PUBLIC QUESTION: Right.

DR. BROWNE: Now whether you use Dr. Murphy's specific RT-PCR test or you use a limited space assay to measure it, that's up to you, but you know, it might make more sense to use his because it's available and you show that it works, but you could use whatever assay you want. You just need to show that it works.

PUBLIC QUESTION: Okay, great. And then, I'm really glad you did it having used both PCR and smear to diagnose people in CHMI. No one should be using smear going forward, but my question is philosophically. You were funded by the Gates Foundation to do it and I think many of us are glad you did it, but what's the incentive to a researcher who doesn't have that funding to do this? Is the agency considering how to make it attractive for, who are the incentivizers for that?

DR. MURPHY: So we, I mean, we really couldn't have done this without the foundation's support, and I don't think that this fits into like hypothesis-based research that is the norm at NIH, though I think the NIH should consider that if there are biomarkers that cut across the needs of like a whole field, that they ought to consider funding as the same way the foundation did. It cost a lot of money to do this work, you know, to support these people over the time it took to do this. So we would really advocate for that, but there would have to be some process to figure out what biomarkers we're talking about. You know, one of the things that struck me yesterday is that a lot of the biomarkers we're talking about in how vaccines work are still, I would, I guess in my view are in the discovery how do vaccines work phase. And whereas this biomarker is in the did the vaccine work or didn't it work, is the patient protected or not. They are two very different things, and I could see, there were talks yesterday about how the mechanism of one antibody delivered by a certain vaccine when trying to make the same antibody with a different vaccine actually didn't give you data that necessarily matched up. So it would be difficult to go down the qualification road only to find out that your immunologic biomarker

has a very narrow scope of what vaccines it can actually be used for. And so figuring out which immunologic biomarkers are going to fit the needs of everybody in this room is probably cause for another meeting.

PUBLIC QUESTION: All right...

PUBLIC QUESTION: Sorry. If there are no questions here, there is one question online as a follow-up to all the biomarker questions. This is to Dr. Sarah Browne. Given the proprietary nature of private industry, does CBER research include biomarker research/qualification?

DR. BROWNE: Yes, I mean, I think a lot of the work that we do encompasses biomarkers. As we've heard, they really run the whole spectrum. The qualification program is really just a formalization of how we define biomarkers for use in drug development.

PUBLIC QUESTION: Okay, thank you. I think someone named Barbara responded to the previous person who raised a question in terms of the incentive. They mentioned that there is a funding available from UTA for developing biomarkers for applications somewhere in the early stage, and I asked for the specifics but I haven't heard a response yet. Thanks. There are no questions for the...

DR. BROWNE: Thank you.

DR. MURPHY: Thanks.

(WHEREUPON, a brief recess was taken from 10:19 a.m. to 10:44 a.m.)

MR. ROBERTS: Okay, let's get started with the last session before lunch. If everybody can make their way back to their seats. Okay, we're going to start session five about practical considerations and this is a really good segue from the previous session. Let me just do a couple of housekeeping things first. I hope everyone was able to fill out the survey, and if you haven't yet, you still have time. We will be collecting them in the back to the left right before lunch, and we'll go over those and those will inform the discussion for the final session with the external stakeholders. So you still have time but do not leave without leaving your survey back there. The other thing is that

June Wong, who is monitoring the Adobe Connect, is going to make an announcement for those of you who are watching online and invite you to answer some of these survey questions and submit them in an email to June. So she will make that announcement online and make that a possibility for everyone who is attending remotely. The one other thing is that I want to remind the participants in the final panel discussion to join us in the speaker room, we can tell you where it is before lunch, at around 1 o'clock and we can talk about what we've heard from this survey to give you some sense of where the discussion might go in the final session. So with that, we will get started with this session and I'll just invite to the podium our first speaker, Nathalie Garcon, who will talk about, the title of her talk is all with respect to adjuvanted vaccines. So, thanks, Nathalie.

DR. GARCON: So good morning. So we have some disclaimer to do, the previous speaker said that when he submitted his data to a gentleman, they said he was boring. I hope I'm not going to be, I probably will be boring because I'm addressing the same thing, but I pray it won't be too boring. The second thing is actually we have seen a lot of token biomarkers looking at one type of biomarker at a time, so we are going to go one level beyond where actually I'm going to talk about biomarkers and what school system biology where you actually integrate a lot of different biomarkers to see if you can identify a print that would actually serve the purpose that you're looking for with its predictive follow-up or follow-up of treatment or of cure. Okay, so system biology, another way to correlate is to understand that the whole is bigger than the sum of the part, and basically what it means is if you take a genomic, transcriptomic or immuno omics, all type of omics you can think about, what is of value is integration of all those that are together and what it will give you as an answer rather than looking at each single one of them and adding them to get an answer. So it refers to two that are used to follow the host response to vaccination, integrating data from genes to its product and beyond, in light of the neural system in particular. And those that are used to be the multi-scale of the models that will, with a goal of identifying a limited unmeasurable viable which are the biomarkers, that we'd allow you to predict the efficacy and safety of a vaccine following vaccination. And I was pointing earlier, you

validate a biomarker. The way you measure it after is up to you to the technology platform you want to use. It's a biomarker that you measure, and for that, the technology you use to discover, assess, and validate can be anything, and it may not be the one you will use to measure it later, and that's important. So what is the best approach to biology and population? There are several questions actually that I think that one can ask, which is, is it the best way to analyze a biological sample from the naïve versus a vaccinated individual if that's efficient or should also or rather look at healthy versus infected, or even better, look at recovered latent versus progressive disease. Those are probably closer to the reality than when you get to the naïve and the vaccinated individual. Do we fully understand host pathogen interaction at the population level, at the individual level, and do we fully understand population viability? And one can ask the question when you design and evaluate a vaccine, should you, and you want to improve a vaccine, should you rather focus on the extreme responders so the one that responds well and the one that do not respond, rather than the average can understand improve on vaccine and allow the population specification. And that's where biomarker will and can be identified. And finally, that brings a complexity of the data where you need to use the right technology for the right question, and actually when you're embarking to that, to have a clear vision of what you want to do, how you want to do it, and what you want to measure because it's very easy to get lost in many things that are completely irrelevant, and that's not the easiest way. So for, so I have to talk about adjuvants, and in the context of adjuvant, understanding their mode of action, it certainly can help interpreting safety and efficacy data, and I have seen that, that knowing the mode of action, if you do not know and it's more difficult to understand whether should a mechanism involving adjuvant and in particular what is considered as adverse event or potentially a particular adverse event you could see in the context of an adjuvant. When you know it, on the other hand, it certainly can help to conclude whether a vaccine or adjuvant could cause a particular adverse event, and that's a biological possibility or in use of long-lasting protection. So in both cases, having those data certainly help to define, understand how your vaccine work in terms of efficacy and safety, but also can help you improve vaccines that are not fully

and completely protective. There are challenges when you talk about metronomics, so we talked a lot about one omic. Now if you talk about gene transcript protein metabolic immune response adverse event, clinical, biological, then you enter a realm of so many data and so many things that you really have to be structured and know what challenges you're facing and what you have to do to be able to get an output that will be of value. And that's start by the experimental challenges. The sample preparation has to be reproducible. That seems so obvious but so complex. You need to make sure that you always have the same sample prepared the same way so that you can generate the same results. The study design, the whole producibility, the reputability you assume you are at a steady state, that's an assumption but you have to make it, and the statistical power of what you are doing is key to be able to generate data you will be able to interpret. Then you have all that is the individual omics data sets so you normalize and transform. You can have to do imputational strategies, so when you have a gap, you fill it. You have to be aware of the platform specificity and sensitivity, which are prerequisites somehow if you want to build on discovery of a biomarker. Then you have all the integration of your data that may serve issues. You have, you need to scale, sorry, scale and reduce your data, the statistical tools you're going to use, there are many of them and I certainly am not an expert in that, the false positive by design, the unknown are known so you know them when they come. When you get with three or more omics data type, that's when it can become complex. The correlation measure, the anthology, and we talked about that and the enrichments analyses also are key. And then once you integrate, then you have your data, and for your data, the workflow and pipeline are critical. They need to be defined prior in the analysis. They are fair principal so it's, I don't remember, they have to be, your data have to be accessible, recoverable and in such a way that this is not data you use only once when you do that, that exercise but you can reuse them later in other integration and analyzing that you're going to do. You need to be able to archive and share, and also you need to think ahead of the visualization you're going to do on your data and usually that require that you write your own program and system. And finally, which is the end part you're looking at which is a biological knowledge. So

how are you going to interpret the results you see? You are hoping to discover a biomarker. You will most likely not validate those targets in the preliminary study that will be done after words on targeted analyses in different study. You need to ensure the usability of your database. This is not the type of study you do, and build a database or warehouse database that you will just use once, so you have to make sure that you can reuse it and you have to look at the possibility of phenotype prediction. So there's a lot of challenges that you face. It doesn't mean that you cannot work around them. So I will give you an example of a project that I started a year ago now that we do in collaboration with Center for Pasteur which is an integrated approach to see if we can answer some of those challenges in the context of new adjuvants integrated with recombinant attention. And the gaps that are seen, for which answers we would like to have answers are what is the value of predictive model. Can we predict the reactogenicity or the efficacy of a vaccine in a specific population or in each individual? Can we confirm or infirm the value of clinical species for translational to human including reactogenicity and can we develop a rational design approach of the vaccine adjuvantation. So that's a very nice wishful list you have to shoot for. So Mosaic it's a five-year project, so we started last year and actually last year and a lot of this year was to set up to do the different experiments, so you'd have to do a lot of preparation. So it's a study that I am to advance vaccine molecular signature in the immunogenicity for those adjuvant and safety profiles for ultimately make our approach in clinical species as well as in human. So the problem really is there is a limited prediction of safety and efficacy of vaccine and adjuvant vaccine in particular. What has changed, the thing and the game changer is that there is clearly an increased knowledge of the innate immunity and in particular the effect of adjuvant and innate immunity and its link with adaptive immunity. There are more and more new technologies that are available to assess omics at many different levels from a very, very small blood sample to the amount of data you can generate. And there are also an exponential decrease in the ability to analyze massive data from machine running to artificial intelligence. So what is applied in that project is to try to have the risk approach from next generation adjuvanted vaccine by identifying specific and across adjuvant type

biomarkers, increase the understanding of novel adjuvant mode of action, assess the predictive value of clinical species for translation in human, as I said earlier, and that then hopefully you'd be able to rationalize adjuvant selection for a given vaccine for, targeted to a specific population. So a big part of the other thing has been the technology development. You do not embark, as I said, you want to have validated assays, so you have to make sure they are validated for what you're looking for. And a big part has been done especially on the sample preparation and biobanking with now the ability to do on one single sample multiple analyses on minimal volume so that allow to, first you show always your assays the same and that increase of the immunodeficiency. In parlay to that, there is a biobanking that is done and which is adapted to diverse and additional analysis, so you cannot do somebody pointing out the cost of those things and this is, nothing to say about the cost. It's tremendous. So you have to prioritize the biological question you have, but you can do biobanking on specific samples so that you can add later, those type of analysis either with existing technology or thing that will improve over time. Now we need to assess more technology for the question we have, and the question we have offset for us before we start. We do a generic question once, we added that up. That's certainly tempting, but it doesn't work, and we, those questions now, amongst other things, the pre-vaccination studies of local reactogenicity and that goes beyond histology. You can now use alternative technology and that's in any modes look at the inflammatory lipids that are present at the injection site at the time of recovery and the mode of recovery, for example. And then you optimize omics technology so that you can use them for consultation approach applied to that project, and that is a very heavy focus on data management and analysis within and across species. And that's a few words but I think the biggest and heaviest focus is on that data management and the analysis that we're going to do. So the objective for the pre-clinical in vivo model is to identify passway trigger by different adjuvant associated with vaccine antigen, so I didn't tell you it's one recombinant antigen with three different adjuvants, one of them being already analyzed in the vaccine. And we want to see if we can find early biomarker of immunogenicity and safety, and when I say early, ideally and even better before you vaccinate, that will

predict what will happen to population or to individual. So the rabbit study is designed as closely as possible to the repeat dose toxicity study. Why? Because this is something you do for regulatory purposes and as to the safety of the vaccine, but there are probably better and more predictable ways to do that in other settings, knowing that in the context of adjuvants in particular, both mice and rabbit may not respond to a specific adjuvant the same way that you would respond in human. Likewise, a mouse that is closely or as close as possible to the human trial and the monkey study also is as close as possible than the human clinical trial. Clinical research trial, evaluating and analyzing the safety and the immunogenicity is classical in clinical trial, yet the setup of such a study is, require a lot of effort. There are medical time point sampling, especially during the first week after vaccination, being a study that looks in particular to the innate immune response, you have to be able to assess within hours of vaccination at the initiation of the vaccine schedule. Identification of early biomarker and pathways certainly one of the objectives and especially which is in use from the first vaccination so that there will be a heavy biobanking of blood sample after other vaccination, but the focus, initial focus would be on the innate immune response, and that would be 250 subjects, so five groups. One controller adjuvant, two different adjuvants at two different doses, with vaccination at zero, then two months, then six months. So there has been a strict and well-defined flow of experiments and analysis and we are trying to control as much as we can so that we are not, we are but we try not to be tempted to do other thing and then what has been set forth for that study, and so the accord recurrent definition of the validity of everything was done of course like for any trial, sample acquisition, biobanking, metadata collection has been defined, and the clinical trial should start at the end of this year. The clinical sample and the analysis that will be done, we are not doing genomics. It will be transcriptomics, proteomic, metabolomic, immunomic, and I can go on. And for that, we have made sure that the technology we use are state of the art method and equipment that the sample and the analysis protocol are standardized and validated, and the equipment and ration are reliable and will be available for the length of the study. And that for all of that we can demonstrate robustness and reproducibility. One you have generated all

those data, you have to resist the temptation of doing analysis on the run and you have to do them when it's, you have collected everything that you need and you go to bioinformatics, biostatistics, not biostatistics. And for that you do routine analysis, data management, analyzes in integration and in correlating and once you have done those analysis that are usually more one type of omics across species, then you can move to multiple omics between one species and so forth and so on. Then you go to what is, the part that is most likely to generate print and the biomarker that could be of value, which is biostatistics and machine learning, for which there you need to apply advanced analysis, you start to do biomarker analyzing, mechanistic insight, translation and then application of those biomarkers because the idea is not to generate knowledge. The idea is to generate biomarker that will be of value for pre-vaccination, post-vaccination, and will help define improvement of a vaccine or define which population are the most amenable to be vaccinated with a given vaccine or a given adjuvant. So I said that earlier, but the data management and analysis is a key to the whole project, and the thing to remember from that study is that there is a unique information repository that is being beefed which is a data warehouse that, for the continues data integration and analysis. So every single data will be, will stream into that data warehouse whether it's coming from the different animal species relives the human data through if everything will stream into that warehouse and they have to be organized and set so that you can ask all the questions you want. You can retrieve them, you can reuse them, and they are classified in a way that they are useful for your intent. So then once you have all your results, you have your data that will be organized within your data warehouse, then you have to see how you're going to, what type of analysis you're going to do and how you're going to integrate. And here the challenge is really the large volume of data. There will be a lot of different data that will exist, and basically the more data you have, the more combination of analysis you can make. It's exponential. So you really have to make sure that you have clarity in the question you want to ask and that's an exercise that has been done and completed now where all the biological question that are intended to be asked in that trial have been defined. They have been defined and validated and there has been a process that has been put in place whereby there's

a flow that's up here that will, oops, was done for, there for each study there is a description of that study and the common vocabulary, and that was touched upon earlier. You realize that when you have biologies to metabolic people, immunologist, statistician, they all use the same word and it doesn't mean the same at all. So that has been a lot of exercise too to make sure that everybody was understanding the same when they were using words for each of those study. There is a glossary that has been put so that we are sure that everybody says the same thing about the same thing. And then ID cards have been built and this is also the heart of the whole exercise. There is a definition of a high level data analysis strategy, so you have the question, you define the strategy and then the strategy you want to use, and this is to, it's a combination of observational, valuable as well as omics and those you define what you're looking for, what you will use to do your analysis, and then you build an ID card for each biological question where you have, this is a key document which actually will follow the experiment all along where you define the first study, you study the experiment that will be done, the species that will be involved, the samples that will be involved. And then for also everything that is prerequisite and the input you're looking at and as an output you have the analysis strategy, the expected results, and the format in which you're going to have that output. So it's boring because it's very well organized I guess, but it is really, sorry, it is really critical when you want, you cannot just do, go with the idea of, I mean you can look for biomarkers, of course you can, but if you want to look at biomarkers that will have health value for prediction follow-up, defining when people won't be protected anymore, you need to be very rigorous in the way you're going to go from A to Z. Make sure that you have defined the question you want to ask before you start because, and I've been there, the temptation is great when you have data to go sideways and see if you have something else than what you want to look at, and you cannot do that, and this is actually the beauty of one single data warehouse. You can do that after because the data will be there and they can be reused. So you have to stick to your initial plan. So we hope through that study to address most of the challenges that exist for biologic, system biology, what won't be addressed, false positive, we know them when we've been, well, in a bigger study, and known,

I think it's Rumsfeld who said there's a known unknown to, the known to known unknown and unknown to known or something like that. Anyway, so we won't know the unknown and known and we will face them when we see them, and the validation of the targets will be done in a bigger study because this one, you cannot claim that with fifty people per group you will have all the answers to all the questions you're looking at. So what we expect in 2022 is to have, there is the approach for our next generation vaccine candidate that will use adjuvants by identifying specific and across adjuvant type biomarkers, increase the understanding of the adjuvant mode of action as a predictive value of clinical species for translation to human including reactogenicity. And for this one, you can see the next step, which would be to do organ and shape and single-cell analysis that will be much more close to what you will be looking in human if it's done in condition that include the dynamic and reproduce really what's happening in human. So and all of that is for rationalized adjuvant selection that will be adapted to the target petition in the vaccinated population. Thank you.

MR. ROBERTS: In the interest of staying on time, we'll come back to whatever questions you may have. So we are going to have now a couple talks about GBS, and Barbara Mahon from the CDC will get us started.

DR. MAHON: Morning, everyone. All the slides are being pulled up. I'm going to be talking about a study that CDC is sponsoring, case control study here in the United States that is aiming to identify antibodies reasonably likely to be associated with protection from young infant invasive group B strep disease. And I'm speaking on behalf of Stephanie Schrag, who is the principle investigator and who knows the study well and is responsible for what we're doing. So I'll do my best to give you correct and complete information, but might need to go back to Stephanie if there's detailed questions. So first, just a quick review of young infant or neonatal invasive group B strep disease. This is one of the invasive syndromes caused by streptococcal bacteria. Pneumococcus is another very important one. But GBS is especially problematic in young infants. It causes sepsis, meningitis, and pneumonia, which can either be invasive or non-invasive. In the U.S., mortality is still about 5%, even

with all of the excellent medical care that we have. In other countries with less resources, it's much higher than 5%. So there are some other perinatal syndromes that are associated with group B strep infection, stillbirth, maternal invasive disease, and possibly premature delivery. The incidence is up to three per thousand live births, so quite a high incidence, and importantly for what we're going to be talking about for vaccine development, there's five serotypes that are responsible for almost all disease around the world. The most important are serotype 1A and 3. Other important serotypes are 1B, 2 and 5. So we divide young infant group B strep disease into kind of two categories. So the first is early onset disease, and that's disease that by definition occurs, has onset in the first seven days of age. This is from maternal colonization and exposure either in utero or during the birth process, and you see the graph on the right here, this is from South Africa, but before we had prevention in the U.S., looked very similar here, shows the days of age at onset for early onset disease. And you can see that most of it is on the first day of age. There's also late onset disease, which is also important. That's onset at seven to eighty-nine days of age. That can be from vertical transmission, but it can also be from horizontal transmission, not necessarily from the mother. And whereas the early onset disease can be prevented by the intrapartum antibiotic prophylaxis strategies that we use in the U.S., the late onset disease is not prevented by those strategies. This graph shows the week or month of onset of late onset disease. So what you see is really the, it's skewed very much toward the earliest ages. So our current prevention strategy as I mentioned in intrapartum antimicrobial prophylaxis. About 25% of pregnant women, give or take, are colonized with group B strep, and intrapartum antibiotic prophylaxis is highly protective against the early onset, against early onset disease. So here in the U.S., we started implementing screen and treat strategies in the mid-1990s and saw a decrease in early onset disease. That's what you see here in the red. Those were then modified for universal screening in the early 2000s. And you can see how the early onset of disease rates came down dramatically to meet the late onset disease rates. But the late onset disease rates really just haven't budged. So WHO does recommend IAP for GBS colonized women, but that's easier said than done because even in high income countries, implementation of these

screen and treat programs and achieving adequate treatment before delivery is very challenging. And in much of the world, it's really completely infeasible. There may not even be the readily available technology for screening. There's also concern about exposing a fairly substantial proportion of deliveries to antibiotics, so there's obviously the selective pressure for emergence of resistance but also concerns about the effects that exposure of newborns through that treatment could have on the neonatal microbiome, which may have much broader effects even beyond resistance. And so, there has been a discussion within the group B strep research community for many years about whether maternal immunization could be an effective strategy to prevent young infant group B strep disease. So the foundational observation is illustrated in this figure from Carol Baker Seminole, a paper from the 1970s, which is that among infants that are known to be exposed to group B strep, the mothers who had higher antibody titers and recall that maternal antibody is actively transported cross the placenta late in pregnancy. So babies are born with an antibody repertoire that is similar to that of their mothers. The babies who, this shows just serotype III, babies who were exposed but did not get sick had higher titers to the capsular polysaccharide of serotype III than babies who were exposed and did get sick. And this observation has been repeated multiple times in many case control studies, many settings around the world. So it's a robust observation. However, there are a number of limitations to these data. So these studies have tended to have small sample sizes. The methods for inclusion and exclusion have varied, as have the methods for actually doing the immunologic testing. The assays haven't been standardized and no standard analytic method has been agreed upon. Nonetheless, the people who work on group B strep disease have been thinking about, you know, what it will take to move this field forward. And a couple of years ago, a supplement was published with a series of papers showing the potential impact of a maternal vaccine that was safe and effective. This is one figure from that publication estimate that there are 319,000 invasive young infant group B strep diseases with more than 90,000 young infant deaths globally in 2015, and that a vaccine that was eighty to ninety percent effective thus could save about 66,000 lives by preventing 230,000 diseases annually, so potentially high impact. The status of

candidate vaccines in development, the primary approach has been through protein polysaccharide conjugate vaccines, and these are serotype specific capsular polysaccharide based vaccines. The current candidates are either pentavalent or hexavalent, and in phase I and II studies have shown good safety and immunogenicity profiles and good maternal-to-infant antibody transfer ratios. So we are aware. We've been talking about for the last couple of days that the feasibility and cost of phase III trials is a real barrier to moving this field forward. So for efficacy trials that have disease endpoints, it's estimated that more than 40,000 pregnant women and their newborns would need to be enrolled, and this is really a high bar. So in May of last year, FDA convened an advisory committee, Jeff mentioned this yesterday, to talk about group B strep vaccines, and there was agreement that this was an unmet medical need. And the committee expressed openness to consideration of licensure based on immunologic endpoints. So some of the considerations would be that standardized assays will be critical, and the assays that have been under consideration are anticapsular polysaccharide IgG and opsonophagocytic killing assays, and there's a group B strep assay standardization consortium that the next speaker will be telling you about in detail that aims to standardize and validate these binding and functional assays to make the assays and associated reagents available publicly and to convene research groups using those assays to contribute to establishment of immunologic endpoints to support vaccine development. So I'm not going to go through all of the details on this slide. I just wanted to show you that there are four case control studies that are currently underway that are part of this group of researchers that are aiming to develop these immunologic endpoints. So you see that these studies are in two developed countries, the U.S. and the U.K., two developing countries in Africa. Two of them are underway, two are in planning. They're using a variety of design approaches. They're all case control studies but with different designs, and they have different specimens that plan to be collected. What all of the specimen plans have in common is that there will be a group B strep isolate from the sick case infant available for serotyping. There will be a measure of neonatal antibody levels at birth, and there will be demonstration that the mother was in fact colonized with group B strep of the specific serotype. So in the U.S., we are doing

one of those case control studies. The rest of my talk is about the design and implementation and considerations with our study. So our general approach is that we're conducting an unmatched case control study in the U.S. CDC's active bacterial core or ABCs surveillance platform, and I'll tell you a little bit more about that on the next slide. We're planning for three years of active enrollment. We started earlier this year and are going through the getting traction period of working out the kinks with the sites. We will be using for this study the residual newborn screening dried blood spot, and this is a picture of a poor little baby getting its dried blood spot taken. So as you probably know, essentially every infant in the U.S. has a dried blood spot obtained for newborn screening for a variety of conditions and inborn errors of metabolism and so forth, but the dried blood spot, the filter paper has, they collect more blood than is needed and that filter paper is then stored in case additional testing is needed for clinical reasons or potentially can be available for research. Our primary objective is to describe the group B strep invasive disease probabilities associated with a range of antibody concentrations at birth, and the goal is to enable GBS vaccine development, as I've described. So a little bit more about the ABCs surveillance system. ABCs is a, it's part of CDC's emerging infections program, and it conducts surveillance for invasive bacterial infections. Not just GBS but also pneumococcal, group A strep, H. flu, meningococcal, Staph aureus, a variety of other pathogens. In ten sites across the U.S., this is laboratory-based, population-based surveillance. So and several of the sites are complete states; other sites are part of states, but in all of the sites, the entire population is under surveillance. This amounts to about forty million people, little bit more than that nationwide. For our GBS study, eight of the sites will be participating, and in those eight sites, there are about 430,000 births annually. For our study, cases are defined as babies who are less than ninety days old with group B strep isolated from a normally sterile site, typically blood or CSF. The samples that we'll be using include the group B strep isolate and the residual newborn screening dried blood spot. Some of the details of how the dried blood spot will be used will vary by site. So the regulations are state specific for availability of dried blood spots, residual dried blood spots for research, and also those rules have changed recently and seem to be

in, they changed several years ago and have changed again recently. So they're in sort of a, seems like a constant state of flux. But at some sites you need individual level informed consent for using the residual blood spot for research. In other sites, with recent changes in the common rule, it actually may be possible to use the blood spots without individual level informed consent in a de-identified fashion. For controls, they're defined as mother-infant dyads in which both of the following are true, so that the mother was colonized with group B strep based on her antenatal screening, and the infant did not develop invasive group B strep disease. And remember, because we're doing this in ABCs, we will know whether the baby developed group B strep disease or not. The samples for the controls include the colonization isolate from the mother and the residual newborn dried blood spot from the baby. And the recruitment of controls will be site specific, so newborn screening, I'm sorry, antenatal screen and treat for group B strep is basically implemented nationwide. It's the U.S. standard, occurs at thirty-five to thirty-seven weeks, so the lab or clinic that's doing that screening might generate a list of group B strep positive women and then recruitment could occur either in person or by telephone, and we are aiming to include one or more high volume clinics or labs at each of the sites. So for data collection, and again I'm not going to go through all of the details here, but the point is that we are gaining most of our data from the labor and delivery medical record, and that includes both antepartum maternal intrapartum and infant data, including underlying medical conditions in the mother, which is something that we added on the advice of FDA during our consultations with them. And we will know whether mother has had fever or chorioamnionitis at delivery. For babies who develop in basic group B strep disease, we will also be abstracting their hospitalization record from when they are treated for that. And then from the newborn blood card itself, we will have information about whether the neonate received a blood transfusion before the blood spot was taken. Over our three-year enrollment period, we expect to enroll about 415 cases and about 2,350 controls. We are aiming for a one to three case to control ratio, and we will continue control approved recruitment until we achieve that. We need to have that over enrollment of controls for serotype specific analyses because, for serotype III, which is one of the most important. It's

more common among cases than among controls. So in this table, I'm showing just some of the expected case numbers for different strata of overall early onset disease, late onset disease, a couple of the serotypes that we're looking at, and again we will be looking at other serotypes beyond these, and then all just spatial ages, more than thirty-four weeks, less than thirty-four weeks. So the point here is that although more than four cases is a lot of cases, by the time you get down to some of the specifics of analyses that are interesting an important, the case numbers do start to get pretty low. So some of the strengths of this study are the use of the ABCs platform. So this is the largest invasive group B strep disease platform in the world, and so, and it identifies all of the invasive group B strep within the defined catchment area, and we have other data from audits that really shows that we're very close to a hundred percent. We also have the ability to capture the relevant infant and maternal information, and we have access to the group B strep isolate. So those are important strengths. And then there's just the general efficiency of building on this program and taking advantage of the newborn screening program to conduct what essentially is a study of a very large, extremely large birth cohort. But there's also some significant limitations and challenges, so the case control design doesn't allow us to directly estimate disease probabilities for given antibody concentrations, and so that's an important limitation. The representativeness of the study population is a question mark. The ABCs cases are population based, but the cases that agree to enroll in the study may not be, so we hope to get a very high enrollment and hope that if we're able to enroll, cases without, the identified cases without consent that that will help with that. The controls are not going to be representative of GBS colonized pregnant women, and we're not going to be able to evaluate in what ways they're different from GBS colonized women overall. There's also some limitations related to using the dried blood spot. So there's a very limited quantity of blood in that blood spot. The original assays that have been developed have been developed for use in serum, so we're going to have to do bridging studies to use the dried blood spot. There's concern that the card substrate itself may inhibit the OPKA. And then the stability of blood spots that have been refrigerated for some time for these assays isn't known and will need to be

evaluated. There's also the possibility that we're going to be able to enroll some retrospective cases to increase our case numbers. So the vast, the great majority of the cases will be enrolled during the three-year period. But we might be able to use retrospective cases to supplement. So we would look at sites that have, that store their dried blood spots refrigerated. Maryland and New York qualify and we will need to do some stability testing to make sure that this is feasible or to evaluate whether this is feasible before proceeding by including those cases. So another set of limitations relate to the IAP strategy that's in use in the U.S. So there's the possibility of misclassification because the controls will have been screened and will have been known to be colonized with group B strep. It's likely that the majority of mothers of controls will have received IAP. Therefore, they would have been cases. We don't think this is going to be a large problem because the number, because we've been able to estimate the number of controls who would have been expected to have become cases, and that is quite small, so about nine of the five hundred for serotype III, about four of the three hundred for serotype Ia would have been expected to have been averted cases. There's also the concern about generalized ability because it may well be that receipt of IAP plus the antibody titer leads to protection that's different than what the antibody titer alone would have done. So in November of last year, we had a telephone call with FDA. This was an informal call, an informal discussion where we just went over the study and they had had a chance to look at the protocol in advance and were very thoughtful and very generous in their sharing of their thoughts on strengths, weakness, potential limitations, and things that they thought that we should consider in the protocol. And this will really serve as my summary slide. They agreed about many of the strengths that we, that I've talked about, so they agreed, or strategies that I've talked about. They agreed that serotype specific estimates are going to be necessary. They agreed that it's a good idea to look at early onset disease and late onset disease both individually as well as together. They agreed in a focus on serotype III and serotype Ia but also expressed interest in the other serotypes, which are important causes of disease, though rare. And they agreed with what we had proposed, which was to prioritize the ELISA over the OPKA. And that was both because the original studies that showed

protection from maternal antibody titers were done using binding antibody, but also because of concern about the impact of the substrate on the performance of the OPKA. And they agreed with us that a maternal sample was not necessary to achieve our study objectives. They urged us to include infants less than thirty-four weeks of age to the fullest extent possible and we are trying to do that. And they talked a great deal about the need for looking at these issues related to the performance of the dried blood spot, bridging stability, the impact of the matrix. We talked at some length about the potential impact of IAP in terms of averted cases being included in the control group, and we talked about potential statistical analytic approaches. To cut to the chase there, they were open to a variety of approaches and expressed willingness to look at a statistical analysis plan. So we found all of that very helpful, and I'm going to, the next speaker is going to talk more about the development of the assay, but I'll just stop by showing that funders and the study sites, this is founded by the Gates Foundation as well as the CDC through the National Center for Immunization and Respiratory Diseases, and the study sites are listed there. So thank you very much.

MR. ROBERTS: Thank you very much, Barbara. We'll move to the next speaker so we can stay on time and save some time for discussion before lunch. And I see that Kirsty was able to join us. There was some question about that, given her need to attend another meeting at which this same topic was discussed. So we're very glad that you were able to join us, Kirsty, and I'll just turn it over to you.

DR. MEHRING-LE DOARE: Okay, great. Thank you. Good morning, everybody. I think it's still morning. I've sort of lost sense of days and time, I'm afraid. I'm going to give a brief overview of some of the work that has gone into standardization of assays to try and measure antibodies against group B streptococcus. So we've heard about group B streptococcus and what it is, so just to add to what Barbara was saying, it's a normal gut commensal, and this is important in terms of thinking about the immunology. It lives harmlessly in up to 25% of pregnant women, but it's also present in male guts, and it's only a problem during the birthing process when in the absence of

intrapartum antibiotics, up to 50% of colonized pregnant women can pass GBS to their babies. And then up to 2% of babies can suffer from sepsis and meningitis. The burden of disease we've already heard from the previous speaker, but just to say that in terms of global sustainable development goals, group B streptococcus is a key priority if we really want to target the approximately 50% of deaths in children under five that occur within the first twenty-eight days of life. So what is the role of antibiotic in protection against group B streptococcal? You've heard about the different studies that are going on looking at natural antibodies, so how is this thought to protect? So going back to group B streptococcus being a normal gut commensal, it has a variety of immune invasion mechanisms that either evade the immune system or help invasive potential, and the key targets for vaccines at the moment are the capsule and then some of the key proteins here, the alpha C proteins and the pilus proteins, and I'll come back to those later. We know that if we're talking about a maternal vaccine for group B streptococcus, what we're talking about in terms of protection is IgG. IgG is the only antibody that crosses the placenta. There have been various studies which have demonstrated that placental transfer is optimal from the third trimester and that these antibodies not only cross the placenta in quantity but also functionally active in the neonate and young infant. As we've heard, the group B streptococcal, search for a vaccine has been a labor of love for Carol Baker for the last fifty years. Her initial study which we've seen identified layer antibodies against the GBS capsule associated with the increased risk of neonatal infection in the 1970s, and yet we still don't have a vaccine against this key disease in the neonatal period. And one of the problems is we can't really decide on what protection looks like. So this is a study from the UK from 1990 demonstrating male and female controls. Mothers have colonized infants, so infants without disease; mothers of infected infants, so these are infants with GBS disease, and these are just any other antenatal patient. And here you can see that there are low antibodies in mothers of infected infants and lower antibodies also in colonized infants, and this study suggested that 2 micrograms per mL was associated with protection against serotype III infection in this UK population. Great, we're getting to an idea about what protection might look like. However in South Africa, this

large study from 2015 from RMPRU looked at cases controls, which are women colonized with the same serotype who don't have infants with GBS disease, and women colonized with any other serotype. And this is serotype Ia and this is serotype III, and you can see here antibody is lower in cases than in controls, but actually the antibody, so 2 micrograms per mL and you can see here on the scale that actually this is around 0.01, so what is a relevant cutoff is a bit of a moot point. Carol Baker and her colleagues then have tried to model to try and understand whether we can actually pinpoint what a sero-correlate might look like that is serotype specific, and here you can see the fiftieth centile and the seventy-fifth centile for a basin model, and the risk reduction associated with increased polysaccharide concentration. And this model predicted 70% overall risk reduction in the USA for concentrations in maternal serum of 1 microgram per mL, and this is 90% for serotypes Ia and III and 70% for serotype V, and you can see here that's because the seventy-five confidence interval is quite wide. Using the same model in South Africa, the risk reduction is 80%, however with far higher antibody concentration, so greater than 6 micrograms per mL for serotype Ia and greater than 3 micrograms per mL for serotype III. These studies were all done in maternal blood, and if we're thinking about a correlative protection to prevent against neonatal disease, actually the correlate needs to be predictive within the infant itself, but there have been far fewer studies that have looked at infant disease. We know that transplacental transfer of IgG subclasses can be less than 100%, and we know for GBS disease that this range is from between forty to seventy-five percent of what's in the mother. Studies by Lynn and colleagues have demonstrated an infant serum, but 4 micrograms per mL is associated with risk reduction against, 70% risk reduction against serotype Ia and 7 micrograms per mL against serotype III, so approaching those figures in the South African women studies. But then in South Africa when they looked at neonates, they found protection associated with 0.5 micrograms per mL in the neonatal serum. So this has caused an awful lot of headache for anybody trying to understand what a sero-correlate of protection looks like. One of the main reasons for this is that all of these studies, as with so many studies of immunology, use different assays and different reagents. So, sorry, use different assays and different reagents, and I'll

talk about some of the key constraints that that provides a little bit later on. I mentioned that there were also some key proteins associated with protection and there are also protein-based vaccines in manufacture, so I thought it was worth discussing the very few studies that have looked at these. And here this is anti-rib and anti-alpha proteins, and there's an adjusted odds ratio of 9:9.2 with increasing low titers of antibodies against those key proteins in the neonates. And here, this is a South African study looking at the pilus proteins, and again, although this doesn't look at a risk reduction, you can see that in early onset disease cases, there is a lower antibody concentration than in the controls for the pilus island proteins. So there is an indication that these might be also protective antibodies. However, the South African studies didn't find any correlation between the pilus protein, island proteins in further studies. When we're talking about protection from the infant, it's not just the quantity that's important, it's also whether the antibody actually works. And there have been several studies looking to correlate the concentration of an antibody measured by an ELISA type assay when opsonophagocytosis. And here you can see in the GSK Fibrini study, there is good correlation for serotypes Ia, Ib, and yes, so Ia and Ib. Sorry, that should be three but I've put the wrong picture in. I apologize. So that's disease. There are also thoughts that we might be able to pinpoint a correlative protection against colonization, so I thought I would summarize those studies quite quickly. This again is the Fibrini study looking at antibodies associated with colonization for four serotype Ia, Ib, III and V, and you can see here that the non-colonized women, which are the gray spots, have lower antibody than the colonized women. It's worth pointing out that this is only a snapshot and what this doesn't tell you is what the functional quality of this antibody is, nor do we really know what the relationship is between serum antibody and colonization. In another study from South Africa where they looked at both concentration and function of the antibody, they actually found that higher concentrations of serum antibody in women was associated with absence of colonization, and they pinpointed a target of 1 microgram per mL for serotype III, serotype V, and 3 micrograms per mL for serotype Ia and III. In the studies that we've undertaken in the Gambia, we found something very similar, so opsonizing antibody was far higher in

non-colonized Gambian mothers and in their infants than in colonized mother and infants. And that's represented here with the blue spots compared to the red squares. We have to remember if we're talking about a vaccine that mothers also lactate and they could use IgA, and this is another study from the Gambia looking at the potential role of IgA in breast milk, and we found that IgA was associated with clearance of colonization. So if the infant was born colonized, high concentrations of IgA in breastmilk over the first few months of life accelerated clearance compared to infants that received a low concentration of specific IgA. There have been far fewer studies looking at the proteins, but mucosal immunology suggests that the proteins might be more important in vaginal protection. We know that the rib and alpha-C proteins do modulate invasion, but there have been no studies looking at correlates of protection there yet. So what about vaccines? So this again is Carol Baker's study. This is pre-vaccination and post-vaccination, and this is just really to say that you can boost with a tetanus toxoid vaccine quite effectively antibodies serotype Ia and Ib. And this is a study from South Africa in Malawi looking at different vaccine concentrations, and again you can see here that this is pre-dose. The majority of women boost and that this antibody concentration is well-maintained. If we have added sort of correlative protection to that, so 1 microgram per mL would be somewhere here, so you can see that post-vaccination the majority of these women have that response. The South African 5 micrograms per mL is here, so still there's a good percentage of women that would achieve a 5 mcg per mL response. For GPS disease, we're talking about protection for quite a short course of time. We know that GBS disease occurs between zero and eighty-nine days of life and then it seems to disappear, so it's important to think about the half-life of the antibody. And here you can see post-vaccination, high concentrations of antibody which remain fairly high but decline actually quite rapidly over the first couple of months of life. And this blue line again here just demonstrates the 1 microgram per mL cutoff. So although there is a quite a rapid decline, those infants would still remain protected if 1 microgram per mL really was the sero-correlate. Looking at the protein antibodies, so this is the unpublished study by MiniVax. Here you can see the different antibody subclasses and IgA and serum. And this again is just to say that there

is good transplacental transfer and that post-vaccine the forward increases are up six-fold for the alpha and rib proteins. So what of assay development? So if all of these assays have different reagents and different starting points and different analysis methods, it makes it very difficult to understand and assimilate that data in any meaningful way. If we're thinking about antibody concentration alone, there are thirty-four different assays in the published literature using different starting reagents, different statistical analysis methods, and different machines. And anybody working in a lab knows what a headache that can be. So this is where the problem really started. And if we're talking about opsonophagocytosis killing, there is still nine different assays using different cell lines, using different complement sources, different analysis methods and different starting and titer calculation methods, which makes all of the studies that we've talked about difficult to translate into any other setting; and we don't know which one is best. So I lead a consortium that is funded by the Bill and Melinda Gates Foundation and directly imported to Public Health England in Porton Down, and we're developing multiplex immunoassays for the quantification of antibody and opsonophagocytosis killing assays. There are standard reagents which we will then be depositing at NIBSC that will be freely available, along with the protocols from these assays at the end. The wet labs are our lab at St. George's then at Porton Down, the CDC lab in the USA, and RMPRU in South Africa. We also have input and expertise from all over vaccine manufacturers making the different vaccines currently available, PATH and Biovac and of course the WHO PDVAC group. So the critical reagents are the things that we think are going to be key to getting assay standardization moving. So for the MIA, this will be the polysaccharide and multivalent reference serum and for opsonophagocytosis it will be standard strains with a reference serum, HL-60 cells because we find them more reproducible, and anti-baby rabbit complement. The standard human reference serum that we started with was Carol Baker's monovalent vaccinee serum using the tetanus toxoid vaccine from adults vaccinated with five different serotypes, Ia, Ib, II, III, and V, and this is the concentration of antibody by RABA that she calculated, so total antibody IgG and IgM for each of the different serotypes. So the multiplex immunoassay uses very similar technology to

anybody who is familiar with pneumo technology that uses the Luminex platform, it uses microspheres that are coupled with PLL conjugated to the polysaccharides. It requires the reference standard that we have talked about, and the key issues of how we multiplex that and avoid interference between the different polysaccharide capsules and the specificity and the precision. And this is just some of the, oops, wrong button. This is some of the readouts that we get from the Luminex machine. It's very easy to use. When we're preparing Carol Baker's reference serum, obviously this, although these are vaccinee serum, if you remember at the beginning, I said GBS is a normal gut commensal, and this means that there are also naturally-occurring antibodies in this serum to non-vaccine serotypes. And when we measure this in the assay, you can see that for Ia, there is also a large amount of Ib and some II, same for Ib. In serotype II, there is also some other serotype and similarly for III and V. and this means that when we are pooling the serum, we need to take into consideration these other naturally occurring antibodies, partly because they will behave differently and partly because the quantification estimates that we had originally are only for that homotypic serotype and not for all of the other serotypes. For antibody unction, we're looking at antibody mediated protection. It's important to consider the interaction of all the antibodies on the surface of the bacteria and the bacteria's ability to fix complement, and we've spent quite a lot of time assessing the strains that are laid down at ATCC and from other sources to try and find optimal strains that aren't very, very complement sensitive and that behave in a reproducible way within the assays. And this is because of those virulence factors that I was talking about early on and the fact that many of these strains are able to either turn on the alternative pathway or they're able to avoid complement binding by different means. And this is our final opsonophagocytosis method, so we have GBS and serum in the final dilution of one and thirty-two, which is incubated for thirty minutes at blood temperature before adding the HL-60 cells and human-rabbit complement, and that's incubated for a further thirty minutes and then it's plated onto blood agar plates, incubated overnight, and then we read it with normal colony count software. And we report titers as the dilution at 50% killing compared to the control serum subtracted from any background. And this

is where we have got to with our consortium. The first stage was to identify and develop the reagents and do a landscape analysis of all of the assays available so that we weren't reinventing the wheel if there was a good assay already out there, and we've had some great help from the Nom Lab at UBC, certainly for the OPER with his years of experience with the pneumo assay. The second objective was to standardize protocols for the MIA and for the functional assays using the standard reagents and to develop independent standard assays with freely available reagents and protocols that will be housed on the internet for people to download in the same way as the pneumo assays are. We're currently in an interlaboratory phase where we are running a proficiency panel across the different laboratories to test specificity and precision of the assay and to look to define the limits of quantification and detection, and Luminex, as I'm sure you know, is very, very sensitive. So it's, we also have to try and determine what the lowest cut-off level is within the Luminex. So in summary, I hope I've demonstrated that it's predominantly Instagram but also some IgA that is key to protection in neonates from GBS disease and that increasing antibody levels are protected, but that that concentration of protection may vary between serotypes and that's why serotype, sero-correlative protection needs to be serotype specific. It may be that as for pneumo we're able to predict for the predominant serotypes Ia and III first and have an aggregate sero-correlate based on those, and then over time develop sero-correlates for the rare serotypes. And as Barbara said previously, the vaccine pipeline will be greatly accelerated we think, if we can actually pull this off. Thank you very much.

MR. ROBERTS: Thank you, Kirsty, and if you can actually stay up here and I'll invite the other speakers to join us at the front. As you are making your way up to the front, I'll just start us off with a question mainly for Nathalie, but if the other speakers could weigh in as well, I'll be interested to hear. I was not familiar with these principles for data management characterized by this acronym FAIR, so just looking that up briefly, findable, accessible, interoperable and reusable. It sounds like there's a sort of a theme across these principles that is important to make decisions about metadata in advance of acquiring the data. And so what I wanted for you to reflect on now if you could

is, I know you're not maybe a bioinformatician, but to what degree do you think about these issues? How important are they for applying them across your organization and do you have any sort of lessons learned from your perspective?

DR. GARCON: So you're asking about all those challenges that I described, first I don't have an organization and it's in the context of that project that we're doing collaboration for always Sanofi but that's applicable for any type of study or design you want to do when you want to do system biology was exponential and reliable that we use. The, you really I think, that's what I said at the end, you, I was talking recently, I think this is the difference between knowledge generation which is entropic and knowing the endpoint you want to reach and you have to do contraction. And for that, you need to define clearly from the beginning what put you on at the end and how you, which step you're going to have to follow to reach that, and what are the work log that you realize to surpass when you do that and especially, it's very easy to drown in a sea of information, very easy. And when, like in that study when we have five different omics plus immunomics plus reactogenicity plus clinical symptoms plus, that's a lot of things to be integrating and there's no way you can do that other than by machine learning and artificial intelligence and those principles which is at the end, they happen to find that you generate so much data and this is such a resource at the end that you need to make sure that you have a data warehouse that is reusable, that the data, as they're organized, you can get back to them and ask a completely different question, and this is what basically that fair principle is. You have to make sure that they are reusable, that they cannot be adapted to other question and other analysis. This is a lot of work for informatician, bioinformatician, biostatistician, which I am not. But I know it's a lot.

MR. ROBERTS: I think this is a recurring theme in the quote, unquote real world evidence space, as well, that many of these data sets can't speak to each other and I think we're going to face that problem increasingly for all the data that, these huge data sets that were...

DR. GARCON: And that's what we are trying to do.

MR. ROBERTS: Do either of you want to speak to the issues of data? Okay. All right.

PUBLIC QUESTION: Perhaps a follow-up on this in term of big data analysis and things like that and given the fact that we are logistic session here, when Nathalie, on some of the study that you're pursuing with Sanofi could you tell us also like on adjuvant specialty, it was also that IMI funded project called BioVacSafe where you wanted to find like a correlate of reactogenicity, you know, coming from different vaccines, and one of these vaccines was adjuvant AddaVax. So could you comment the lesson learned in term of logistic from BioVacSafe and what you could do, what you could not do or should not do from that lesson learned?

DR. GARCON: I can only comment I was not at GSK anymore when the BioSafeVac protocol went on, so the only thing I've seen is what has been published, and if you look at the outcome of the program is, I don't think is as expected or delivered that would have been expected to see the amount of data that were to be generated, the number of vaccines that we're testing and the way it was done. I cannot comment on why. I wasn't involved, so. Maybe you were.

PUBLIC QUESTION: Yes, but I think one of the specialists take home message was like not an obvious reactogenic vaccines in this cord. However, there was some signature that has been found, you know, from BioVacSafe in term of correlate of, you know, reactogenicity even though it was not obvious, it was not serious adverse event. So do you intend also to use this type of know-how where it's like this transcription analysis that we've been able to do and also to apply with the mosaic program?

DR. GARCON: So if I remember, one of the reactogenicity biomarkers was CRP. Biomarker by definition needs to be discriminative and we need to be able to tell you with a sufficient level of certainty that the position you're looking at is the one you're targeting. CRPs, I mean, it varies. I mean, you bend your arm against the wall, you're going to have an increasing CRP. It is not what I call a specific biomarker for reactogenicity. So in that sense, it was expected somehow to have

those type temperature variations. They did show actually there was a trial evaluation which was also expected, which at the end labeled everything back to about the same level. The most reactogenic adjuvant was not that reactogenic anymore, so it...

PUBLIC QUESTION: But that...

DR. GARCON: It's a shame, frankly...

PUBLIC QUESTION: Yes.

DR. GARCON: ...because there was so much effort put in it.

PUBLIC QUESTION: However the studies including clinical trials, you've got to be able to interrogate from BioVacSafe, you will be able to combine this data at certain points.

DR. GARCON: It depends.

PUBLIC QUESTION: Yes, depending on...

DR. GARCON: It depends how they're being collected and how it has been stored also.

PUBLIC QUESTION: Just one question also I should be asking, I think one of the presentations by CDC specialist was like maternal sample not required to achieve steady objective. That was one of the comments from Siebert and I'm a little bit surprised given the fact that the last presentation where the antibodies, transfer of IgG is so important for protection for strep B. Could you comment on that?

DR. MAHON: Yes. Because we will have the newborn screening blood spot and will be able to measure the antibodies in that blood spot, we will know what the, basically what the infant was born with, and of course that reflects the endpoint of a, you know, maternal antibody production and transfer across the placenta, et cetera. But we do have that, and that could, you know, be variable from mother infant across mother-infant dyads, but we will have that measure from the baby. Almost all of those samples are taken within the first twenty-four hours of life, so I think in many ways it's, you know, it's sort of an ideal specimen. I think we're more concerned about the blood spot itself

rather than, and you know, the problems with that that I mentioned rather than with this of not having a pertinent measure of kind of what antibody the baby had onboard. Kirsty, do you want to, do you have anything to add to that?

DR. MEHRING-LE DOARE: No, I think that's about it.

DR. MAHON: Okay.

DR. GARCON: There is something, there's one place where you could reach the database is, it's mining of the literature. There are ways now to mine the literature, not, through words, actually. You do word search through the literature and you can be in a position to access data that way that you would not otherwise.

PUBLIC QUESTION: Yes, especially when the transcript told me...

DR. GARCON: Yes.

PUBLIC QUESTION: ...that it's not just the value of microgram per mL but...

DR. GARCON: Yep.

PUBLIC QUESTION: ...that full change that you could enter, that should match or should bridge over the study.

PUBLIC QUESTION: Nathalie, I have misunderstood, so you need to clarify something for me and I may or may not ask my question, but so this mosaic project, so is, I think I understood this correctly. So you're looking at three different adjuvants...

DR. GARCON: Mm-hmm (indicating affirmatively).

PUBLIC QUESTION: ...and you combine all three adjuvants, I mean each of it is the same vaccine antigen, right?

DR. GARCON: Yes.

PUBLIC QUESTION: And so the goal is not only to arrive at a biomarker predictive of safety but also immunogenicity/efficacy?

DR. GARCON: Yes.

PUBLIC QUESTION: So I'm struggling with that concept because if you look at three different adjuvants, adjuvant A, B and C, and you combine adjuvant A with antigen X and adjuvant B with antigen X, I mean, isn't one of the principles, I mean, you've got, the adjuvant is supposed to enhance the immune response to the specific antigen.

DR. GARCON: Yes.

PUBLIC QUESTION: And of course can perhaps also redirect the immune response that is induced by the antigen alone. But if you look at the biomarker, let's say a new biomarker, maybe you arrive at one, wouldn't this be in part at least driven by the specific antigen, i.e. not?

DR. GARCON: That's a good question. There's a paper that was published two years ago maybe where the, given it was in animals, not in humans, three different antigens, three different adjuvants, and the bottom line is that the immune response innate and adaptive was driven by the adjuvant...

PUBLIC QUESTION: Mm-hmm (indicating affirmatively).

DR. GARCON: ...not the antigen.

PUBLIC QUESTION: Really? I guess I'm going to have to rethink.

DR. GARCON: I'll send you the paper.

PUBLIC QUESTION: All right. That's the components...

PUBLIC QUESTION: Whether it's by that antigen.

DR. GARCON: Yes. It's a recombinant antigen.

PUBLIC QUESTION: Well, the repercussion...

DR. GARCON: I will provide you the paper.

PUBLIC QUESTION: How can you extrapolate that biomarker to, you know, if you, you know, let's say you arrive at one for a specific adjuvant...

DR. GARCON: Yes.

PUBLIC QUESTION: ...I mean, can you easily apply it to the different adjuvant-antigen combination. That was my question.

DR. GARCON: So on, usually, yes, that's a good question. That's a very good question, yet you do see, you take two different adjuvants with the same antigen. You do not have the same output.

PUBLIC QUESTION: Mm-hmm (indicating affirmatively).

DR. GARCON: Yet you take the same adjuvant with two different antigens you may have the same input. So it's really the adjuvant that drive, and most like the innate imprints you give at the beginning that will, after that, the quantity will be defined by the antigen. The quality of the antigen will define the extent of what you will see, but the starting point seems to be really what you induce as innate immune response.

PUBLIC QUESTION: Okay, thank you. I have another question. Can I ask if you've done any group B strep topic? So it's very interesting and I know we, you know, many, many years have really gone in to try to define a correlate of protection, but I'm sort of struck by the data that you showed where you looked at antibodies thought to be protective or predictive protective and you looked at different populations. So there was a stark difference between the South African versus the vast population. Do you really think, I mean, what are your thoughts, what really in that specific field need to settle this population specific critic predictive biomarkers?

DR. MEHRING-LE DOARE: I think it's a good question. I think the key problem that we have is, up until now, we just haven't had any standard reagents, so you don't know if this is a true population difference or whether actually this is all just a problem with the methods. We've got four large seroepidemiology studies and now that we have a standard assay, we'll be able to look at that specifically. And yes, then it might be that we have to say in a high-burden setting like South Africa where they have high pressure of bacteria and other co-morbidities, that it might be that it's a different sero-correlate to other populations.

PUBLIC QUESTION: Thank you.

MR. ROBERTS: So let me just ask really quick to stick with GBS for a minute. I wonder if you guys could speculate on this. We're surprised so many times when it seems clear that something's going to work when it doesn't. And I thought Ted Pearson's talk to start us off was so fantastic, just demonstrating that seemingly the same antibody doesn't work, and I wonder if this doesn't turn out to work, you know, vaccinating the mobs, what, could you speculate on what you think the mechanism might be? I mean, potentially for example the mom has an immune response that we're not measuring that could affect the quality of the inoculum in ways that maybe don't have anything to do with the antibiotic. Any thoughts around that? Where, what might be we looking at now to try to head that off at the pass?

DR. MEHRING-LE DOARE: It's a very good question and I think it's a really understudied area. So the meeting that I have just come from has been trying to look at exactly what those questions might be because you have the other's immune response, you have the way that the immune response reacts with the placenta and how whatever it is crosses into the infant, and then you have the infant's own or the fetus's own immune response and how that reacts to what antigens or antibody or other immune factors come across. I think it's a really, it's one of those things where you think systems biology might have the answer, but I think we're not quite sure what the questions are yet.

PUBLIC QUESTION: I have a clarification question that maybe after that another one for Dr. Mahon or Dr. Le Doare. So in your CDC study where you're collecting samples and maternal sample among mothers who were colonized and who did not transmit disease, the mothers were colonized and do transmit group B strep. And you mentioned that you, the controls did not include others who were not colonized as a control, and I was just wondering, did I get that right or if that's true, why did you not include those controls?

DR. MAHON: I think I got lost during the question, I'm sorry. So the controls are all colonized, mothers.

PUBLIC QUESTION: Right.

DR. MAHON: Yes?

PUBLIC QUESTION: That was my question. Why was it, why did you not collect the samples from mothers who were not colonized? Because those mothers will not get the part of antibiotics and they may actually be immune to the colonization itself.

DR. MAHON: Yes. Well, to some, this is an oversimplification, but those babies are also not at risk of getting certainly early onset group B strep disease. So if they can't, if they are not able to present as a case, then they're not suitable to serve as a control. So it's a little bit more complicated than that because the late onset disease hasn't, the children with late onset disease haven't necessarily been exposed through their mother. They could have been exposed through another root, but that's a smaller number of cases. And so for the early onset question, the answer is that, you know, that it's sort of, they're uninterpretable because they don't have the exposure that would lead them to actually get the disease.

PUBLIC QUESTION: Right, but in trying to develop a correlate protection or biomarker, it would be of great interest to know those mothers who actually don't have any risk of transmitting group B strep, and those might include those who were not colonized for whatever reason. They're not exposed or they have some sort of immunity to group B.

DR. MAHON: Yes. So I think you're getting at some of the, you know, greater complexities of group B strep sort of ecology and, you know, colonization comes and goes. A mothercould be colonized with different serotypes at different times. They could be colonized when they're not pregnant. And so it's a, we're sort of taking, trying to make some simplifications to be able to do the study. But you're right, I mean, the overall biology is much more complicated than our kind of simplifying study design would imply if you kind of extrapolated backwards from that about how do we think group B strep acts. Kirsty, do you want to add anything to that?

DR. MEHRING LE DOARE: Yes, well, just to say from a purely logistical point of view as well, if only 20% of the pregnant population are colonized and you actually want to extend that out to the whole population, your sample size increases exponentially, which makes these studies really big quite quickly. And if you can't guarantee exposure at that time, then you're not sure exactly what it is that you're measuring.

MR. ROBERTS: We're getting close to time here. Let me see how we do with the next question.

PUBLIC QUESTION: Hi. My question is for the mosaic study. So it would be obviously great if you found kind of single biomarkers that were predictive, but I was curious, you have an opportunity to look for complex combinations of biomarkers. I'm wondering what the implications, both from your perspective of those types of findings and perhaps also from the FDA perspective kind of the willingness to consider those more high-dimensional answers with your high-dimensional data.

DR. GARCON: So I doubt that would be one biomarker, so it's more likely there will be several. How many I won't guess. Complexity, I agree that increase of complexity for the use and the validation and probation of such test, the next step is, and that's the complexity of it, you move from an addition of assay to what you can call a hand print, and you have that image that represents what will be the marker of the efficacy of the reactogenicity. I think that's a completely different world of assay, not development but assay of agitation, and that's probably a bridge that's going to have to be crossed at that time, but it may be the only way to have predictive markers from a specific event. So I'm sure statistician will make it.

MR. ROBERTS: The question is multi-dimensional data, this is a good one. We're convening a meeting to talk about that specifically and I can give everyone more information about that. I think we're going to have to stop here unfortunately because we're really going to have to be back on time at 1:15 to get started with the last session. And I'll just remind everyone, if you haven't

finished your survey, please do that and drop it off as you leave on the left in the back. Thank you. And thanks to our speakers. Fantastic.

(WHEREUPON, a brief recess was taken from 12:20 p.m. to 1:21 p.m.)

DR. GRUBER: So good afternoon. It's time I think to convene for the last session entitled state quota perspective on current and future uses of biomarkers in vaccine development, licensure, and post-licensure surveillance. And we have invited stakeholders from different organizations to really give their perspective and their thoughts regarding this field. So I also wanted to let you know that over the last one hour, we tried our best and our darnedest to analyze and read through the responses to all survey questions that we posed to you, and there were really sort of interest comments made and response provided, and I think we sort of heard a common theme. But in these forty-five minutes, it was just not possible to really do an in-depth analysis of it. So we're going to do this over the next couple of weeks when we are back in the office, and I think we're going to reflect the analysis in the meeting report that I mentioned yesterday we were going to write. But what we're going to do today is really as our stakeholders give their perspective, Sarah is going to flush out the PowerPoint presentation a little bit and then we're going to project them at the beginning of the panel discussion to give you a little bit of a view on what the responses and suggestions looked like. But again, it's qualified because we didn't get to every response. So what I thought we can do is, and to try to be this, to make this all a little bit more informal, is to invite our stakeholders up and join me here on the panel. Then you don't have to stand behind the podium and give your perspectives, but I leave this entirely up to you. I just think it would be great if at least one or two people could come up here and I'm not so lonely. How about it, Jeff? I hate to sit here all by myself, guys.

FEMALE: Let's go with her.

DR. GRUBER: Yes. Please join me. Okay. That's much better. I think it's much better, so, yes. And so I think, see I really purposely wanted to talk and talk and talk to get the room full of people again so that Phyllis didn't really have to, you know, give her remarks when people

are walking back into the room. But anyhow, our first person giving her perspective is Phyllis Arthur. She is with the Biotechnology Innovation Organization, Bio, where she is the vice president, infectious disease and diagnostics policy.

MS. ARTHUR: So first, thank you very much for inviting me to represent industry on this very important topic. Obviously, I think you heard in all the presentations from industry members and scientists that this is a really important topic obviously. Companies in the vaccine development process use biomarkers and assays for many different things, but there's a lot of interest in seeing particularly where this new, this field can take us in terms of some of the, in terms of the Context of Use for some of those diseases that are maybe not as easy to do large clinical trials. So there's definitely an interest in looking at how biomarkers can help reduce the time and complexity of doing trials for epidemic and pandemic diseases. There's definitely a strong interest and better understanding of how biomarkers could be used for safety purposes to either be predictive or to be helpful in terms of understanding better what the safety signals may be. One of the things that everyone has been talking about on our side is certainly, and you hear this from us all the time, Marion, so smile now, is guidance. We do one of those things, that's why I do that smile, I know that smile, because every time we meet we ask for guidance and she smiles like that. I think there's a strong interest in the industry in having an understanding how long the process is for validation, what kinds of data would be helpful in validating a biomarker, when to start, where does it go. And so as always, because you're working on multiple programs at a time, guidance from the industry coupled of course with the individual excellent meetings that people have across the phases is one of the things everyone was interested in. There's a desire in particular to have more harmonization and standardization not just across varying vaccines in a certain area or across certain bioassays, but also across regulators. One of the hardest parts is how do different regulatory bodies view biomarkers in the clinical and approval process, and certainly can there be, through consortia and through CEPI and through other processes, ways of getting the acceptability of them up across some regulars that are not as comfortable with them as the EMA and FDA. And then I

think that there are a couple of other issues that came up. One of them is the connection or how we think about biomarkers in the context of the regulatory process and then acceptability of them and the data generated by using them in the recommendations process. So these two things are, I think there needs to be some thought as to how using a biomarker particularly as a surrogate for a normal clinical endpoint will, if at all, affect the evaluation of a product by any of the assessing groups like ACIP, both in the U.S. and abroad, that companies have to go through. There's always those two parts. And lastly, I think there's one other issue that had been discussed today that just sparked a good conversation between some of the industry folks is many companies are working on platforms that could be used for multiple different antigens. Is there some process by which validation of certain biomarkers in a platform actually will speed the process of moving from one antigen to another, particularly if you're thinking about rapid response or other kinds of families of viruses where this is another way to standardize and reduce clinical development time when a platform could have the power to work on multiple things? So these are the kinds of topics that we had raised as industry and are really looking forward to discussing with the rest of the partners.

DR. GRUBER: Thank you so much, Phyllis, very helpful. So the next person giving his perspective is David Kaufman, chief medical officer of the Bill and Melinda Gates Medical Research Institute.

MR. KAUFMAN: Well, thank you so much for the opportunity to participate today. This has been a really stimulating meeting. I'll start by just talking a little bit about the Gates Medical Research Institute, which may not be familiar to everybody here. So we were launched at the beginning of 2018 as a subsidiary of the Gates Foundation. I think the simplest conception really is as a nonprofit biotech, though it feels a lot more complicated from where I'm sitting. But our job and our mission is to take products for, by global health indications, into IND enabling studies through clinical proof of concept, and in some cases beyond even into registrational studies, and we're working across multiple indications that include tuberculosis, malaria, enteric diseases, major causes of infant mortality,

and a number of other indications, and we are modality agnostic and so we have vaccines monoclonal antibodies, small molecules, and even devices now in our portfolio. But what we share across the entire portfolio is a commitment to trying to use the most cutting edge translational science tools that are available in order to speed the availability of these potentially life-saving treatments and preventative interventions. In vaccines, our lead program is in tuberculosis where in a few weeks we will be starting a study of BCG revaccination in adolescents. This is a follow-up study to the one that was run by Aris Ensafen (phonetic) in South Africa and showed a very intriguing signal of preventing sustained infection as measured by a biomarker endpoint which was QuantiFERON conversion, and so we're hoping to follow-up on and extend those observations. We have a number of other programs in the TB vaccine space as well as in malaria where we're working on both next generation CSB vaccines that are informed by structural vaccinology approaches as well as on monoclonal antibodies. And then in the Shigella vaccine space, we're working on a next generation quadrivalent O-antigen drive vaccine. Finally, we have a strong interest in understanding adjuvants in a more deep way. We would like ideally to help to speed both bioequivalent and novel adjuvants to the global health market in particular, and we're very interested in making sure that there is sustainable access to those types of adjuvants. But in that setting, what we really are interested in doing is thinking about how to characterize those antigens early on and in new ways with respect to potentially biomarkers that help us understand both pharmacodynamics and safety. So we're working across a large number of spaces from very early development through potentially as I said registrational studies, and we also because, although we're not going to be a market authorization holder, we have to think very carefully about what the needs of our downstream partners are. We want to make sure that we do the right work from an immunological perspective, from a biomarker perspective earlier in development so that if things like immunobridging, et cetera, have to happen later on, that we've set our partners up for success in this phase. So sort of back to all the different contexts that Jeff was talking about at the beginning of this meeting, we think about pretty much every single one of those, maybe even a couple that you didn't mention as we think

about our biomarker program. And so for really a few high-level issues that are at the center of what we think about, the first is we want to get the dose and interval right for vaccines. We would love to bring more model informed drug development principles and more modern approaches to understanding those pharmacodynamic relationships to vaccines. I think that the small molecule field as a whole is well advanced of the vaccine field in this space, and that I think speaks to some of the things that Nathalie touched on earlier in terms of both the way that we do toxicology and non-clinical pharmacology studies and the pre-clinical space, and also the way that we approach measurement of immune responses so that we can have a more gradual understanding of dose response relationships as we start to go into the clinic. We also want to, a second key principle for us is to create more stringent and more biology informed stage gates earlier in development so we can make better decisions. We have more confidence in those early stage gates; we'll feel more comfortable taking more shots on goals and maybe taking riskier shots on goal, and that's really important for us to innovate in our product development pipelines. And so that really requires both taking all of our biological knowledge and putting it into those stage gates, but it also requires a lot of reverse translation. What are we learning in the field that's relevant for our early phase studies? What are we learning in our early phase clinical studies that help us to set up points and validate the pre-clinical models that we're using? And obviously the third big area is to inform actual regulatory and policy pathways that we will take, and of course we're specifically focused on our target geographies and there's a lot of complexity about the intersecting regulatory and policy bodies that are involved in actually getting the vaccines that we'd like to develop to the populations that need them the most. So I can give a few examples, and I think I'm running out of time so maybe I should skip my examples and...

DR. GRUBER: Go ahead.

MR. KAUFMAN: Yes? Really?

DR. GRUBER: Yes, yes.

MR. KAUFMAN: I'll give three quick examples. The first is around the BCG re-vaccination program. So our work is based on the observation that vaccinating adolescents who have previously been vaccinated at birth with BCG and were unaffected at the beginning of the study, prevented sustained QuantiFERON conversion over the course of the phase II study that was previously conducted. It didn't prevent initial conversion, but it did prevent sustained QuantiFERON conversion, and we know obviously that that, you know, that prevention of infection is an important pre-requisite for, it's important for preventive disease. But because infection doesn't always lead to disease, we don't know for sure that preventing an infection is necessarily going to translate into truly preventing disease. And so one of the things that we're very interested in doing in this program is trying to bridge that divide. Are there other things that we can look at? Are there other biomarkers of subclinical disease or impending disease that we can see, that we can characterize and that we can understand if were capable of abrogating with this vaccine to give more confidence that we are actually going to have an impact on clinical disease, which is what we care about. The second example is in the malaria states where we are obviously very lucky to have the kinds of controlled human infection models that have been discussed at this meeting. And there, we want to really use the prior knowledge in the field, and I think while some of that has been silent over the years, there's a number of publications that are coming out soon that I think will really start to provide some more granularity around some of the immune parameters that are potentially important parts of the correlative protection for malaria vaccines, or at least CSP-based vaccines. We want to make sure that we are incorporating those into the assessment of immunity at the time of challenge and then modeling out those parameters over time to try to understand whether we can really meet a target product profile of dermal protection over several malaria seasons. And finally the third use cases are adjuvants program where I think I already talked a little bit about our interest in using some of the tools like what Nathalie was describing to really understand safety, dose, and dosing interval. So I'll stop there. Thank you.

DR. GRUBER: Thank you. So I guess in order to make this a little bit more informal, David, you're going to be the next speaker. If you can just introduce yourself and then you pass the mike to Marco and then I'll call...

MR. KASLOW: You got it.

DR. GRUBER: Thank you.

MR. KASLOW: David Kaslow. So first of all, thank you for inviting PATH to give a perspective on a nonprofit vaccine development and introduction entity for vaccines destined to low and middle income country public market. So pretty specific mission. I'll mention three topics but really only talk to one in any detail. The first one is that these biomarkers, particularly for low and middle income public markets need to provide the evidence to get through, not just the regulatory but the regulatory policy and financing continuum. Otherwise, they're going to get stuck in that continuum and won't actually get to where they need to be used. Recalling that a product becomes a vaccine only when it gets injected into the arm of the vaccinee. And so that's something that we pay a lot of attention to is how will this biomarker get through that full continuum. The second topic that we spent a lot of time thinking about is the post-licensure commitments to establish effectiveness if licensure is based on a biomarker and realizing that the ability to do a robust effectiveness study in the UK for something like group B strep is going to look very different than trying to do an effectiveness study in a GAVI eligible country. But what I'd like to do is just take a few minutes to raise the need for another biomarker. It's apparently not called out as I can tell in the best terminology but that we at PATH experience on a frequent basis, and we've only peripherally touched on it. I think it's your fourth, Jeff's fourth Context of Use biomarker, and that's for manufacturing changes. This gap is particularly acute for conventional vaccines compared to therapeutic biologics or drugs or diagnostics in which there's a good structure activity of relationship and well characterized biologics. Here as we all know, the process is the product. You change the process and you change the product. And so we're finding ourselves more frequently involved in technology and product transfers to an emerging market manufacture in late-stage

development or even post-licensure, but without a regulatorily acceptable surrogate endpoint and potentially facing large clinical trials to do that, including efficacy trials. And so this gap is further exacerbated by the fact that there isn't a well-established, i.e. a clinically validated biomarker, but there also isn't oftentimes a well-established product analytic biomarker, be it a critical quality attribute or a robust potency or stability indicating assay to bridge to. So this gap creates a pretty big challenge for us in developing compelling comparability protocols that allow us to demonstrate the lack of a negative effect caused by any manufacturing changes on the safety, quality, or efficacy of the vaccine. So what's missing? A clear multi-disciplinary approach that connects the clinical research scientist with a process engineer that clinical assay with the product analytic, analyst, and even the clinical assay quality group with a CMC quality group. And we see this as a growing gap that really needs some additional attention if we want to ensure an affordable and sustainable supply of vaccines in public markets in low and middle income countries. So with that, I will turn it over to Marco to get a regulatory perspective.

MR. CAVALERI: And I will answer all your questions, of course.

MR. KASLOW: Perfect.

MR. CAVALERI: So I am Marco Cavaleri from the European Medicines Agency, and thanks for inviting me. Of course this is a very important topic no doubt. Biomarkers are crucial for the development of a new vaccine but also for their regulatory life cycle management, and heard a lot about the number of cases and, you know, and we just heard another scenario where it's very important to think about what kind of biomarker will be used for regulatory purposes. I have to admit that so far we've always been able to handle these kinds of situations somehow, but it's true that, you know, we can always do better and think about how can we improve or how we handle these cases and find the right way of accepting changes in the manufacturing process. But it's clear that for me there is a higher need than ever on having biomarkers for developing new vaccine, particularly in light of what has been already said for emergent pathogens, epidemics, pandemics. We need to think out of the box and consider how we can move ahead with regulatory decision on vaccine that the natural effect cannot

establish efficacy base on clinical trials preapproval. This is an important area and we need really to advance this. There are other areas like, you know, second generation vaccine where also they are conducting clinical efficacy trial for demonstrating efficacy is problematic, and also there it is very important to figure out what kind of biomarkers we can use for allowing approval of this vaccine. As a regulator, of course I always have to say that we need body dated assays that the methodology has to be sound. We need to be convinced that that is what is proposed as an assay platform makes sense and works, and also important for me to stress that even in those cases where you can conduct clinical efficacy trial, it is important to collect sample. I think Julie demonstrated very well with the Zika case that was important during early development, and even in trial, you collect samples as much as you can so that you can then realize and understand whether there is any biomarkers that would correlate with protection or could be used for whatever other purpose. So this is something that we will never stop recommending to developers to think about, and there is a lot of money in doing this, but I think it's a good way of, you know, making sure that you have the sample that you may need in the future so you might be money well spent and I think that's important. As said, efficacy is key and in the vaccine space is pretty obvious, but also safety is important. This morning we heard Nathalie talking about a project but also it was mentioned the BioVacSafe, which was a European project with the public partially funded by the European Union, as well, and a huge amount of data were collected in this project with respect to all the all mix and try to understand what could be, you know, a kind of pattern of biomarkers that would create reactogenicity. Unfortunately, for a number of reasons, it was not possible to come up with anything definitive, and I think also here for me was pretty clear that the lack of good clinical data to match to was one of the reasons why this was not possible. If you don't have clinical data, you know, showing cases where reactogenicity occurred, you will never be able to find the biomarker reactogenicity. So again it's very important that there are also clinical data to correlate to your biomarkers. Otherwise, you will not achieve what you want to do. Maybe also to advertise that at the EMA, we also have a qualification of biomarkers procedure and this can be an opinion, can be in

advice or a letter of support, so there are different options. It has a timetable of 130 days and there are a few exceptions for academia or other consortia that are not from the private sector or from commercial organization. Of course the evidentiary requirements will change according to the context of use, you are fully agree with what my FDA colleagues have been saying throughout this workshop, that's a very important one. And of course we also recognize during all these exercises with biomarker qualification that the evidence required to establish in a lot of cases it's much more than what to establish benefit. So it's very important not to forget that validating a biomarker in certain cases is not so easy. But still, you know, this is a road that is open and we would be happy to discuss that and see what we can do. Maybe two other important points, Jeff rightly pointing out the problem with the terminology, and I think here we got a guide on clinical development of vaccine which we are propagating this confusion because we are coming out with our own definition of a new accords of protection. Sorry about that, but I would agree that we need to tackle this one because there is a lot of confusion also talking to sponsor. Sometimes, you know, they think that we expect something that is not necessarily what we want to see. And so this is another where I do believe that intonation of a corporation and discussion could help in figuring out what could be the best way forward with respect to the terminology. Two points, as David mentioned, of course, and also to reply to Dr. Graham, yes, the CMV vaccine was mentioned and what about post-approval if a vaccine is approved on a surrogate endpoint. Well, it's pretty obvious that we will ask for father effect in the studies. We want to see in the post-approval phase what would be really the outcome on the hard clinical endpoint for which the vaccine essentially is introduced. So I do believe that in the future we will see more and more with the approach of using biomarkers for licensure, the need of establishing a robust platform for effectiveness with good methodology in order to make sure that we are able to collect the data that we want, and also maybe the last point is, since we are experimenting a lot in Europe, is the interaction with the night tech so that the immunization group that will make recommendation on national level, and we are trying to build up more collaboration with them, even at the scientific advice phase so that we can hear from them what they think about

introducing a vaccine in the future if maybe this vaccine will be approved based on a biomarker. We'll be enough evidence this one to allow the recommendation. It's an important question from the developers and we have to work on that. We have to make sure that there is more contact between the regulators and the night tech and also on a global scale with WHO and SAGA. We went through the discussion on the first malaria vaccine, and one of the lessons learned there was that indeed more discussion and dial up with the WHO stage would have been very helpful. Thank you.

MR. KASLOW: So I guess Gary, you're the next one.

MR. DISBROW: So I guess I'm batting clean-up, so I'll keep this short. My name is Gary Disbrow. I'm representing the Biomedical Advanced Research and Development Authority, or BARDA, at the United States Government. We're in the Department of Health and Human Services. I want to thank the organizers for the invitation, and I particularly want to thank all the presenters for sharing all the information in your experiences along the way. So as David mentioned, PATH has a pretty narrow and specific, you know, call for what they're supporting. BARDA has the same, so everything that we do is by legislation, so in the federal government under BARDA, we received funding under Project BioShield, so our investments to address chemical, biological, radiological, and nuclear threats, and we have several vaccine candidates that we've developed for those, have to have a material threat determination (MTD) that is issued by the Department of Homeland Security for us to invest any dollars. So without that MTD, we can't invest our Project BioShield dollars. We also have advanced research and development dollars. We have a little more leeway there and the agents that we invest, medical countermeasures that we invest into address certain agents, but it doesn't make a lot of sense to invest in advanced research and development if we're not going to progress that to late stage development and potentially procurement. So in addition to chemical, biological, radiological, and nuclear threats, we address pandemic influenza and emerging infectious diseases. So to date, our emerging infectious diseases is an unfunded mandate that we have, but we do receive supplemental funding. We did receive supplemental funding for Zika and we've

worked very closely with NIAID and our DOD colleagues on that as well. So we not only form public private partnerships with our industry partners but we work very closely with our USG stakeholders, in particularly NIAID, DOD, other components of NIH for chem as well as the FDA. So you're talking about biomarkers and post-marketing commitments, so for everything that we do, if a product is licensed or approved under the animal rule, because you can't do efficacy trials with the exception of Ebola for the CBRN threats that we're developing medical countermeasures for, there is a phase IV post-marketing commitment. It's automatic. And so we have to fund that. We have to put money on the contract so that the sponsors are ready if an event was to happen tomorrow, that they would have things in place, IRB approvals, and a consortium of clinical sites established so that they could run those efficacy trials. So there is expense with it, but again, it is something that we support. We will also support the development of biomarkers. I mean, that is what we are doing in the development of the MCMs that we're currently supporting, whether it's CBRN or pandemic influenza. I agree with Dr. Graham when he said we need to improve the HAI, we need to identify a new biomarker for pandemic influenza. One of the key things that was mentioned earlier, I think Phyllis mentioned, was reagents and assays. I think it's really critical that you have, you know, identified all the reagents and the assays that you're going to use to develop and support your biomarker. When you go to the FDA, you have to identify the biomarker, explain to the FDA why you've selected that biomarker, have a body of data that supports that. Again, we will partner with you to help get that data, but it is incumbent upon the sponsor to go to the FDA and have that data set ready. One of the speakers talked the other day about the CT, the CD8 response and how you couldn't do that clinical trial, but in non-human primates, they actually pleaded the NHPs for CD8's. So that's additional data that shows that whatever, if that biomarker is C tell, T-cell dependent is that it's very important because you're showing, you know, data both ways that it's important to have it, and if you don't have it, you don't get the response. So I'll just keep it short. I mean, what we do at the Biomedical Advanced Research and Development Authority is support and development of medical countermeasures from advanced research and development all the way through

to licensure approval and for the eleven medical countermeasures that we have that have been approved under the animal rule, we do have post-marketing commitments for all of those. Thanks.

DR. GRUBER: Thank you very much. I thought this was very informative. I think before we now enter the panel discussion, I would like to invite, is it Sarah or Jeff or both? I think you wanted to disclose the results from the survey, and have the slides been loaded? Okay, so are you going to walk us through that from the podium? Sarah?

DR. BROWNE: Sure.

DR. GRUBER: Okay.

DR. BROWNE: Preliminary survey results. Survey says, let's see, what is your affiliation, so total number of respondents was thirty-eight. And you can see the breakdown in terms of industry, there were twenty-one academia and regulatory for each NGO with seven, another was two. Rank, the top three diseases and corresponding preventive vaccines in development for which, I should look here, more data, better validation of biomarkers would have the greatest impact. So you can see basically the bottom line is it's, there are a lot of priorities for a lot of different people. I mean, I haven't broken this down by who responded for what, but the top, we'll say top five are influenza first, TB, HIV, CMV, malaria, RSV, and then others, dengue chikungunya. Question three, areas where use of biomarkers has hindered development or would not be advised. So there were some different diseases that were listed, MTB, bacterial diseases, RSV, staph aureus, diseases of reasonable incidence, HAI titers has been a common theme. Diseases for which multiple pathways, exact mechanism is not understood, possibilities of clinical trials where clinical disease endpoints were not fully explored before the conclusion was reached that the biomarker was needed as an endpoint. So I think leaving the possibility that there could be truly a field efficacy study done. Focus or overemphasis on single non-validated biomarkers can derail product development, and licensing based on a biomarker can preclude obtaining robust clinical endpoint data, and I apologize if I'm not always staying in the same tense. I was typing these pretty quickly. So question four, in terms of advice, I think one of the general concepts

across every affiliation was to collaborate. So I didn't break these down by affiliation, and I don't know if we want to go through each one and have the different stakeholders respond or if I should just read these out.

DR. GRUBER: Just read them out.

DR. BROWNE: Okay, so NGO funders, more funding for confirming clinical benefit after licensure and invest shift more funding to basic research to explore potential biomarkers. Advice for academia was use novel technologies and platforms, explore mechanism of action for rare diseases, consider practicality for assays that will be used by industry and for regulators. So I think this was, practicality was a theme that we saw that, you know, academic assays can't always be translated into useful tools for regulators in the industry and standardizing assays across different research programs. Advice for industry was to take a long view in development to work closely with regulators early on and to try to translate academic findings to product development. And advice for National Immunization Technical Advisory Groups (NITAGs) was to encourage harmonization across sister agencies for global application of vaccines, develop a framework to de-risk use of biomarkers because developers need to know that vaccines developed with biomarkers will be used. And advice for regulators, harmonization across regulatory agencies provide guidance in early stages of product development, continue to educate on current thinking such as workshop and publications and openness to alternative approaches, creativity, and defining licensure pathways. All right, thank you.

DR. GRUBER: Thank you very much. I think there is a lot of good responses here and many things that we can probably have a discussion the whole afternoon on. I would like to really open the panel discussion. Again we'd like to invite participation from the audience, and I also, you know, invite our, my colleagues here at the table for perhaps some, you know, initial responses to these preliminary survey responses that we obtained. And I, since I'm sharing this here, I'm just going to start and kick it off. I wanted to say a couple of things regarding the note that there are at times that the decision is made at a clinical disease endpoint efficacy study cannot be conducted and therefore we

need to use a biomarker to demonstrate effectiveness. And I, in recent time, I've seen this more and more when people, potential sponsors approach the agency, sometimes there's not even a discussion about is a clinical disease endpoint efficacy study feasible. I've seen examples where sponsors come in and say okay, we want an accelerated approval pathway. We cannot do a clinical disease endpoint efficacy study and we're going to use biomarker X to demonstrate vaccine effectiveness. And to me this is a little bit sort of putting the cart in front of the horse because I mean what would be great is really getting a good argument, rhyme and reason why a clinical disease endpoint study is really not feasible and then we can discuss how the product can best be developed. Because I think these discussions are really necessary because of concerns that have been expressed even over the last couple of days that, you know, demonstration of vaccine effectiveness other than in those cases where we have a clearly scientifically well-established correlate of protection leaves always a little bit of an uncertainty about the biomarker really being able to truly predict efficacy. And so there is this issue about how will the product be used, and we had this very example a couple of years ago when we licensed Prevnar 13 in adults fifty years of age and older given an indication for prevention of pneumonia, streptococcal pneumonia. And I remember we had a functional assay, opsonophagocytic assay, and that was sort of the biomarker. But the vaccine was not being recommended until such time that the results from the capital study, the confirmatory clinical study has been conducted with favorable results in the Netherlands. So I think we have to, I think the message that I would like to get across is the agency is very willing to look at biomarkers as a tool to demonstrate effectiveness, and there are examples and there are situations where there is no other approach then looking at vaccine effectiveness by way of establishing a biomarker. But again, the gold standard still is a pre-licensure clinical disease efficacy study to demonstrate effectiveness, and I think we cannot forget that. So thank you. I'm afraid this should have been perhaps my concluding reminder. I really didn't want, didn't mean to be sobering. I just wanted to make that comment.

PUBLIC QUESTION: So you're, if I understand well, you're saying that you could not forget the historical efficacy trials used perhaps many years ago, you know, in term of efficacy and we could, you know, we could use that as an argument to file our vaccines? That's what you're saying? Especially for pneumo, that was really the case because if youcompare to let's say for flu, that's the same thing with HAI and the historical data shouldn't invite that the treasure we were talking about yesterday, the four-four, the one in forty correlate of protection in certain populations. Perhaps not all the time and there's also like a disease, you know, or indication like pertussis, there's that Sweden study that has been done like where we refer to it, so could you comment what you said, you know, about that historical efficacy trial that could be cited when we file vaccines?

DR. GRUBER: I hope that I understood your comment or question correctly. So you're saying that in those cases where we can, where we have an efficacy, a clinical endpoint of efficacy study is conducted with a product and now want to go to a next generation product?

PUBLIC QUESTION: Yes, like a bioaccumulation let's say we have a product that's equivalent that...

DR. GRUBER: Yes. I mean we have been, I mean that concept really is not new and we have been using that. I mean we have been licensing, you know, for instance a meningococcal vaccine, you know, ACWY. I mean these things were licensed in adolescents and adults based on immunogenicity because we were able to bridge to efficacy from studies conducted, you know, years back in infants, right? So we have been doing that and for the pneumococcal conjugate vaccines, I mean sort of the same approach was used. When we stepped from Prevnar 7 to Prevnar 13 to Prevnar 20 and Prevnar X, so yes, that is, and I didn't mean to say I wanted to dismiss the value of biomarkers. I just say, my point was let's have a discussion, let's explore all potentially available approaches to demonstrating vaccine effectiveness before we say we, you know, we sort of, we preempt the discussions and say a biomarker is the only way to demonstrate vaccine effectiveness.

PUBLIC QUESTION: I agree because at this time we have like, you know, the burden of the proof at a certain point when we don't have it yet, you know, like an obvious biomarker, but there's a standard for meningitis it's the SBA, for pneumo it's MOPA, you know like for flu it's HAI. So it seems that all of this indication when you, there's less research on biomarker because you already have established correlate of protection. However, in other fields such as HIV, such as TB as we were saying, I just feel we don't have like a clear correlate of protection, even pertussis at a certain point if any. So where, so this indication will benefit from biomarker. However, I want to say that when you have like a clear correlate of protection, let's say for meningitis, you know, it's SBA. So why not, using that clear correlate of protection to validate a biomarker, even though it might not be useful to use that biomarker for meningitis in co-trials because SBA would be enough. You don't need to go too much fancy in your clinical assay development. So you understand though that my point of view is is there a certain indication that will not benefit from biomarker?

DR. GRUBER: I think I need some help here in really understanding this. I mean, there's an indication that will not benefit from a biomarker?

PUBLIC QUESTION: Yep.

DR. GRUBER: I'm a little bit at a loss here.

PUBLIC QUESTION: Biomarker research especially.

DR. GRUBER: From biomarker research? Well, you know, I think that was captured in the response to the survey, you know, so I think that there are certainly, you know, examples. Although, I mean I wouldn't say give up on it. For instance, I mean I guess staph aureus was listed for a reason, but it doesn't really mean that, you know, the field should give up and looking into, you know, biomarkers to really, you know, demonstrate effectiveness for whatever indication that is. But so, yes. I think, you know, you can certainly come up with examples where, you know, research into biomarkers may just temper the overall development, but my point is still if you can do an efficacy

study, the traditional efficacy study, then I think it should be done because it will settle the question about vaccine effectiveness.

DR. BROWNE: I think that was one of the examples actually where critical endpoints and studies were feasible.

DR. GRUBER: Right.

DR. BROWNE: And also where biomarkers were poorly understood or incompletely understood and had the potential to undermine product development because too much credence was put in their role.

MR. DISBROW: I think the problem here in those situations where you cannot do an efficacy trial and there is not an established biomarkers as correlates of protection, and that's what the problem is. So what you do there, and this is the, we have to work out to figure out what could be the best options that we can put on the table in order to think how we can for the develop and potentially approve vaccines of these kind. So and there are real cases and also depend like, you know, you mentioned pertussis. There are new generation pertussis vaccines that require completely different way to look into immunogenicity. How are we going to navigating to that? So there is a need to work with the agencies to build up the knowledge and what could be the way forward to establish any biomarker that could be used instead of an efficacy trial.

PUBLIC QUESTION: So my question is about what you just said, Marco, and what you said, Marion, about the discussion idea about, you know, so often groups will come to you and say we don't think we can do this, so we want to do this, and you, I think what you said was tell us why you don't think you can do it and then ask us what we think about the next steps; but that sort of goes against what most of us do. We generally don't give you open-ended questions. I don't know if that's how most people feel, but you know, we don't do that and I think that it was nice to hear you say that you'd like to, I think what you're saying was you'd like that. You'd like to have ability to have that dialogue in a more open way. I think that's what I'm hearing. I just want to verify.

DR. GRUBER: Yes, so I think there's one point that I would like to make and that is something that perhaps, yes, I have to admit not everybody in the Office of Vaccines or even at CBER would agree, but many times there is a desire from the side of the sponsor to really, early on in product development to get an idea about what does the overall clinical development program for my product look like. Are you going to require us to do a clinical endpoint efficacy study, you know, can we demonstrate vaccine effectiveness via other pathways, and so some people may argue why would I have this discussion at a pre-IND stage or like early in development when I don't even know if the product would basically pass phase I or early phase II, right? But I think there is merit to have these discussions early on, and then it's sort of like, I think that there's less misconception and misunderstanding. You know, because if you have an early communication with the agency, and we have these means now. It's not only the pre-IND meeting but, what is the other one called? Interact? Whatever that stands for, I still don't know. But anyhow, so we can, you know, we can engage in discussions and sort of exchange information and say what it may look like and what evidence does the agency need to see in order to say yes, we're convinced we can't really do a clinical disease endpoint efficacy study. We're going to have to look at other licensure pathways for this. Let's get some additional data, let's see how that goes. So having these discussions early on I think is of merit because then the company doesn't have to come and say, so we now think it's X and didn't get our early input. But again, I wanted to say I am a proponent of that, but perhaps not everybody is a proponent of that, so.

PUBLIC QUESTION: Hi, Barbara Mahon, CDC. I have a comment and question. It seems to me that if we're increasingly relying on post-licensure studies to actually demonstrate the clinical effectiveness that CDC is potentially going to be a more important partner in some of those programs and just wanted to note that now and just say that, the kind of early and complete communication that has been talked about would be very helpful in that setting, as well. My question is that it seems like another kind of trend to deal with the fact that sort of the low hanging fruit has been plucked for diseases that are easy to develop vaccines with sort of traditional efficacy trials is

to control human challenge models, and those are being developed across quite a number of pathogens, and it's been, people have talked here about how that really is a great opportunity for identifying biomarkers. I'd just like to hear from the panel about, from your various points of view you think about kind of that combination of controlled human challenge models and biomarkers and what the implications are for licensure and for post-licensure.

DR. GRUBER: Okay, somebody else can start. Someone who does clinical development like David.

MR. KASLOW: So yes, I can start. So one of the initiatives that PATH has, that the mode of vaccine initiative has used the controlled human infection model for malaria extensively and I think it's been really great, actually if you down select a lot of things from moving into the clinic. I think it has given us some clues as to where the biomarkers are, but I think one of the biggest challenges is, particularly for vaccines that were developing for a pediatric population is we're in a certain sense forced to do these in a target population that doesn't necessarily represent where we want to go. And oftentimes, although that's changing, you know, they're done in high income countries, we now are doing malaria challenges in low and middle income companies, but it's still not really in the target population and I think this is something that we've really got to sort out is the biomarkers that we develop in that population, how translatable will they be into a pediatric population? Particularly when we know things like polysaccharide vaccines work pretty differently in adults than they do in infants and that sort of thing. So I think it's a way forward but it's still got some bumps. It will still have some bumps.

MR. CAVALERI: Yes and maybe to add that, you mentioned the study as these are important tool and underdeveloped so should be used more in a number of setting and definitely will have a huge impact in streamlining development of new vaccine. With respect to using them for defining biomarkers that can be used for potential licensure, that might be more complicated because as David has just said, there is first of all the target population but also the fact that there's a small study

very well controlled in more dense population, the strain, the dose, there are a number of factors that make them be artificial. So while you can use them to infer protection because you have a direct effect of protection in the studies, and they have been using, will be used is a given. On the other hand, to really use them to define the biomarkers that really matter, you know, they could be very helpful to tell you what could be the biomarker reference but really to establish threshold, things like that, I still see very problematic.

MR. KAUFMAN: And you know I'll second what you guys are saying. It's one tool in a large armamentarium, but what it does is, I mean, it sits in the middle of a space where you can both forward and reverse translate. So I think there's an imperative to get, as David said, to target populations and then reverse translate early learnings back into the stage they are using, so around pediatrics, around hyporesponsiveness, so as we learned in malaria about immune hyporesponsiveness, what can we bring back to immunology earlier on. And then, you know, when you are seeing activity in a CHIM study, being able to design that study so that you can do explore dose ranging, you can understand PKPD relationships and then back-translate that into the pre-clinical assays that you're using to gate going into challenge models to begin with. You've got to have that iterative process.

PUBLIC QUESTION: Hi, Carmen Nass from GSK with a different question here for a situation where definitely it's not an option to run efficacy trials with biosimilars. So my question is whether it's a reasonable assumption that qualified biomarkers should be available in that specific case. I'm not aware of any case yet for vaccines with biosimilars, but I guess at some point that may kick off. And also a second question would be whether there is any plan to generate for the guidance on views of qualified biomarkers for biosimilars.

DR. GRUBER: Yes, that's the, you are absolutely right, we don't really have biosimilars for vaccines and we haven't really thought about that in terms of how can we use, you know, biomarkers to look at biosimilars. I really have to tell you that I can't really speak to that much more than what I just have been telling you. I mean, we have, you know, I mean the argument was made that

vaccines are still, even though some of them you could make a case for well-characterized biological product, but others, you know, are rather complex. And so therefore this, what is the 301K application? I think that's for biosimilars. That's really not applicable to vaccines yet. And the point that I wanted to, you know, and that's the, I have to look up and I would need to follow-up with you because I don't, the licensure of biosimilars in the drug world, is that even through a biomarker? Is it, it's PKPD but I don't know if it's about the biomarker like we sort of have been talking about. But Marco, you may have...

MR. CAVALERI: No, yes. We had a bit of experience so we have to think about it...

DR. GRUBER: Yes.

MR. CAVALERI: ...you know, weigh and indeed for drugs is because, you know, you want to avoid redoing large efficacy trial like in the oncology setting or, you know, rheumatology setting and what you do essentially use PKPD so a pharmacodynamic marker, you put it together with the PK and then if it turns out that indeed it is pretty much the same in specific conditions, then you could use that as your people would update it for approving a biosimilar drug. For vaccine, the point that we already been doing this since many years because when we are vaccines, there are, you know, very similar and we are using the new marker that has been established as the new marker to infer efficacy, and that has been the pathway that has been used. So we may wonder, do we really need to establish a biosimilar framework for vaccine? Based on the experience that we have, maybe not, but of course we are happy to discuss this further and to see if what we're already doing is not enough because I believe that much of what is done with a number of vaccines that, you know, are just new version or version produced by other manufacturing of what is already available on the market, we are applying a little bit this concept of, you know, using immunogenicity to bridge a level of protection, and of course we require an adequate safety database.

MR. ROBERTS: I think it's...

DR. GRUBER: Yes, think you can, can you add to that?

MR. ROBERTS: Yes. This really goes to what David raised in his opening remarks, and I want to explore that a little more because I want to understand what scenarios you're raising here. You know, with Marco saying this is something that we commonly do, one of the examples I thought about bringing up is the JE vaccines in which, you know, a wild type virus formally inactivated process was the basis of the first generation vaccines in a very similar process was the basis of a new vaccine. And that was considered a new product and that was required to demonstrate safety according to our typical requirements, and it went down, it didn't go down the biosimilar pathway. So what is the scenario? Is it transferring technology within, you know, to a satellite organization that would then use exactly the same processes but a slightly larger drone to, you know, make the virus or is it very comparable manufacturing processes that you're hoping to use either analytical or...

MR. KASLOW: That's, it's both actually. So we've got examples of both. And one of the examples is JE and one of the examples is that, you know, we have been working for a long time with CMPG in China at Changtu Institute. They supply 87% of the global supply of vaccine. So if there's an earthquake or a fire or something like that in Changtu Institute, supply comes to a screeching halt. So there's a want to figure out, is there an organization, another provincial institution that you could do the tech transfer to in terms of having a backup. But it's based on a Chinese hamster primary cell line, right? So you've got to transfer the colony and all. So there's a lot of moving pieces there that you want to make sure that you can have a robust comparability protocol. And there I think the critical quality attributes and the critical process parameters are key in terms of the comparability protocol. But we've got some other examples that I'm not at liberty to talk about here where it's not just, you know, it's the whole products being transferred and there's a want to update some of some old processes along the way but not go so far as to distance yourself from the clinical data, but in order to make it affordable and sustainable, you need to make some, I mean it's a pretty delicate balance there. And so additional tools that allow us to do that in a timely fashion without expending additional resources on clinical trials

is critical, it's absolutely critical, and particularly to keep the costs down. So I don't, I can tell you some more.

MR. ROBERTS: I think that would be really challenging...

MR. KASLOW: Yes.

MR. ROBERTS: ...for both sides, but it sounds like something that we, you know, that we could have a good scientific...

MR. KASLOW: Discussion about.

MS. ARTHUR: I think that, the other example, I think is flu and I think that's why flu rose to the top is with regard to innovating from the current way flu vaccines are made which are egg based and evaluating whether the biomarkers and assays that exist for flu right now are actually linked to that, we were talking about this, there's assays that came from the original product. Is there now a problem where the old assay as designed is too linked to a current kind of technology and therefore is inhibiting or hindering the ability to do validation of new technologies made in a different way? And so then either you go through the process of each company trying to do some kind of assay, but then you lose that ability to move quickly on flu and go from one seasonal to another seasonal by having that commonality of a standardized set of biomarkers. So knowing that we're trying to move from egg over time to cell and recombinant and MR, and now the technologies are rife for flu both for seasonal and pandemic. There's a need to really focus on whether or not there's some new commonality for measuring immunogenicity and I think that's going to be a problem for innovation. So a little different vision of it but something that could actually be having a negative effect on the ability to not just move new technology but solve another problem we have on the implementation side, which is demonstrate the efficacy that the whole marketplace is craving, which is why no one gets flu vaccine. We need to find a way to demonstrate that some of these new technologies are going to perform better for flu, and right now everybody's stuck not figuring out how to do that in the presence of the current assays. I think that's a real issue to solve for a big public health issue.

UNIDENTIFIED SPEAKER: We have a comment there.

PUBLIC QUESTION: I'm Paula Nunciato from MER. So one of the challenges that we have when we're developing new vaccines is that at the same time, I'm in the clinical organization, at the same time that we're embarking on the clinical programs including usually an efficacy study, our manufacturing colleagues are determining the process as well as the process parameters and the product parameters, but at that point, they don't yet have enough experience to really know what their process capability is and what type of product parameters they need to be able to sustain the market, should we be successful in our efficacy study. So there's a limited number of laws that make it into the pivotal study and depending on the agency, when it comes to CMC review, the answer we get is, well, those are your specifications and you can't really manufacture based on the experience of those. So I was wondering if you all could talk a little bit about the use of immune markers that aren't necessarily true correlate or protection markers? Because sometimes you just, you know, you're in the good state of having such high efficacy, you can't really know what a true correlate of protection is. How can immune markers and the experience we gave in phase III help our manufacturing colleagues as they're answering CMC questions with regards to things like potency, you know, potency limits, things like their stability limits. And I realize none of your CMC colleagues are here, just, so I promise I won't go back to my manufacturing people and say I heard that...

MR. ROBERTS: Well, I mean, I think there are examples just to raise what you said about being a victim of your own success. You need vaccines so that way you can see among, you know, naïve populations if they respond at all, which they all do, they never get HPV, to keep the rod at a core of protection based on that. So, you know, we recognize that and we really work with the international community and space to try to move to a more reasonable endpoint for future products. And then another example I think of reaching manufacturing is the rotavirus vaccines. You can see that great clinical efficacy was demonstrated, but the best way to measure if immunogenicity is a serum IgA

doesn't correlate very well with efficacy. So, you know, that's another good example of something that can be used to bridge a manufacturing process but that might not necessarily support traditional support.

DR. GRUBER: I, go ahead.

PUBLIC QUESTION: I wanted to reflect on what Marion said at the beginning and sort of throw out some thoughts and perspective. I think currently we always look at the randomized clinical product as the gold standard and it should be, but there are alternative pathways we saw. As far as I know, the animal group is only usable when the traditional approval pathway is not available. However, as Marion pointed out, many sponsors want to use accelerated pathway and I think the reason for that is especially with diseases that are, the trial size is so large that it gets to be hugely expensive, and really what's feasibility to me, we always struggle with this when we're reviewing, is the size of the trial, is that really not feasible, it's only not feasible because of the cost or time. So it comes down to availability of funds. So I'm wondering whether instead of a hierarchal approach to proof of efficacy, you have traditional approval with accelerated. It's really actually use them as equivalent and based on the pathway as it is already existent in regulations, that there is a post-marketing requirement, but the post-marketing requirement for verification could be much more rigorous for accelerated approval using the biomarkers, but then leave the sponsor to choose, whether it's ran like traditional efficacy end point versus an accelerated approval with a requirement post-marketing. And to be very rigorous about it, if you don't prove that it's post-marketing, it could be withdrawn. So in that way, the alternative pathways could be really engines innovation. Now I say this because, and my current perspective is that of a mid-size company developing vaccines, if the burden of proof for safety and efficacy is so high, then what will happen is that only the big pharma will be available to developing vaccines, and that would really make, may restrict ourselves to less innovative, more innovative companies that can contribute to the field. So that's just a comment.

DR. GRUBER: I would like to comment on that, but I'll take your comment first because you have been waiting for a long time.

PUBLIC QUESTION: My comments are along the same lines. Jerry Zada from Janssen. Yes, I was going to make the comment that throughout this presentation, it's always been, well, you could only use biomarkers if you can't do an efficacy trial. But I'd like to make the case to expand like you just did, the use biomarkers and give an example. My company does not make or sell a seasonal vaccine, so I can say I'm not in a conflict of interest to give this example. But take the recent study that Sanofi published in New England Journal on thirty thousand patients that showed that their high dose looked better for a clinical endpoint of high LI. Now the real need in influenza we all know is lower respiratory infection that causes hospitalization. That's why people die. And two years or three years after that study, a retrospective study using Medicare data clearly showed that it was beneficial for that really important endpoint of lowering mortality and hospitalization. So the post-marketing really achieved the goal of what the approach was. Now it took three years of the thirty thousand patient study plus approval so that at least licensure of that vaccine was delayed by at least three years, and we've got the Medicare data within three years, so three years of people being benefited by that vaccine was lost because we couldn't, not we, but they couldn't just do it on a biomarker with some kind of other approval. So my question is why don't we also consider the potential for benefit by faster licensure while we're waiting for the other data which is coming anyway, and much more numbers in the post-marketing Medicare data. That's millions of people getting the vaccine. So that's kind of along the lines that were just said but with a very specific example. And maybe you just can't do that, but I'm just trying to give the case of maybe we should consider that, and that's just one example of many that come up.

DR. GRUBER: So, you know, I mean first of all I think that the influenza, I never really, I struggled with influenza being a good example to be extrapolated across different product pedigrees because influenza really, in looking at effectiveness, presents its own challenges. But for the fuse on high dose, I mean as I recall, that was an accelerated approval and then they had, they did, you know, confirm clinical benefit in a post-marketing required study. So they got the approval.

PUBLIC QUESTION: Yes, but...

DR. GRUBER: And then, yes, but and then the confirmatory study and then there was additional studies which sort of confirmed the effectiveness, but I wanted to get back to perhaps also what Wellington was saying. I think, you know, there is an appreciation from the side of the agency that that large, you know, efficacy studies or safety studies are challenging especially for small and mid-size companies and the cost is always something that factors in. But I think we have, at the agency there's a lot of initiatives that are going on right now. There is not only, you know, yes, let's talk about biomarkers to demonstrate vaccine effectiveness, but there are also pilots and initiatives going on complex clinical trial designs, novel clinical trial designs, so after thinking about how can we actually go away from this paradigm phase I and then phase II and then phase III, how can we sort of rethink the clinical trials or we're all to really demonstrate safety immunogenicity and efficacy. And I think that's a discussion to have in, you know, together is to, you know, biomarker development because I think there are through, you know, fancy statistics, and I'm not a statistician so I'm not going to go into hot water here, but I think there's a lot of stuff that is right now discussed to really see how can we really advance this field. And so that's one point that I wanted to make. And the other thing is, you know, the argument I need a biomarker and then I have an accelerated approval, well, you know, the law requires that confirmatory studies need to be done post-licensure, and my argument is always if you can't do the study prior to licensure, why can't you do it post-licensure? I mean that, okay, that goes into a discussion of evidence and that's another workshop to have, you know, for vaccines, but I mean that's sort of what I struggle with, you know. Because you have to confirm the clinical benefit and if your argument is it's impossible to do a study prior to licensure, then how possible is it to do it post-licensure?

PUBLIC QUESTION: My answer there is the reason most times that it's impossible to do a study with a true endpoint that you're really interested in pre-clinically, pre-licensure, is the incident is too long. Way too long. Incidents of hospitalization in influenza is not 1 or 2% but

maybe .2%, .3%, and that's, you're talking about studies of a hundred thousand patients. So you can get that in post-licensure because not everybody gets the vaccine, and then you can do Medicare and other case control methodologies out of millions of cases, of people, and you can get an answer that's just as strong if not better than the pre. I'm not saying anything was done wrong. I'm just saying maybe we should look at it. That's all I'm trying to say as an example.

DR. GRUBER: No, I appreciate your point, but you know, just a quick answer, this may be true for some vaccines and pathogens but not across the board, right?

PUBLIC QUESTION: No, he's just saying...

DR. GRUBER: Yes.

PUBLIC QUESTION: But I don't know if the situation is as bad as what Jerry is saying it is because we do this and in fact your fluid one of these examples, but there is no requirement that would be impossible to do a clinical endpoint efficacy study if you want to do an accelerated approval. There is, as Marion says, requirement that you find a way to confirm benefit because there is going to be some doubt when the original approval was based on an immune marker, but while with the animal rule, it is required that you not be able to approve through either traditional or accelerated pathways. For accelerated, it is not required that it be impossible to get there from traditional approval. You're absolutely right, if you can get a vaccine out there, make it available sooner under an accelerated approval, that in fact is why the rule exists in the first place. Originally it was contemplated there would be studies going on and you might even be able to confirm benefit through the same study from which the preliminary analysis showed the effect on the marker. And now we're sort of separating those things out, but when it's looking at the confirmatory study, there's something separate. But certainly the thinking about what the confirmatory study is does need to be an intrinsic part of what somebody comes in with if they're requesting an accelerated approval. But to get back to the flu zone high dose example, so as Marion says, that was an accelerated approval. The FDA got that out there pretty quickly based on the immune markers, and then there was the capita study. But when did the ACIP start recommending

it? Well, in fact, it is the recommending bodies that then wait for the confirmatory study before they will recommend that people get it, and in many cases, that will afford the insurance companies will cover it and before people actually end up getting the vaccine anyway. So even if the FDA does approve it quickly, as they did in the very example you gave, then it takes some time for confirmation. It may take some time then for the ACIP to decide that they really believe this, what sometimes that is a, they might view as a higher level of evidence being required to recommend it for everybody versus what we would say was okay for the accelerated approval, and then of course it takes even a little more time than that to show that there actually was an effect on hospitalization and death. And you're right, all of those delays that happen after we approved it were missed opportunities to save lives. But that's all part of the system. I know that this was in the survey and some of our panelists also said that one of the big issues is in fact how can you define a standard for recommending something that actually affects the likelihood that the product will be prescribed from the manufacturer's perspective, of course the likelihood that there will even be a market for the product once it's approved, how can you make sure that that market materializes as quickly as possible, too, if in fact it's a product that is going to save lives, which is of course what the hope is for all of these.

DR. GRUBER: Yep. Still just what I was thinking.

PUBLIC QUESTION: But they wouldn't need a thirty thousand patient trial to show how immunogenicity equivalent to superiority and so they did the thirty thousand patient trial with a clinical endpoint.

PUBLIC QUESTION: That was their confirmatory study. So they did do that with the confirmatory study, but the original study was not nearly that big.

DR. GRUBER: No.

PUBLIC QUESTION: Right.

PUBLIC QUESTION: And they got the approval based on immunogenicity, not based on the thirty thousand patients.

DR. GRUBER: Right.

MR. ROBERTS: So you mentioned real world evidence is something that we're going to need to have a subsequent workshop about, but...

DR. GRUBER: Sign us up.

MR. ROBERTS: ...that is an elephant in this room that I, I would like to hear just some brief initial thoughts from our stakeholders. You know, as I've been involved in agency-wide discussions about this, it strikes me that there's been a lot more, there are a lot more advances from the drug side, particularly in oncology to try to build out systems that go way across getting individual sponsors of best practices standards to try to do this. And so, you know, we've heard from Gary that from an institutional perspective, you guys are putting aside money to do this, but if there's no system-wide approach where you plug in your product and get a good answer, which I would take issue whether we get the same quality of answer from an observation stay as compared to an RCT. I think we have to be careful there, but one of the things that may help is if some of our stakeholders start to invest in systems that could potentially do this, particularly in loan figures so I wonder if you could comment?

MR. KAUFMAN: So in my immediate previous life before coming to Gates, I was working in the immuno-oncology space on some of these cutting edge clinical database tools for gathering evidence, and those tools are absolutely becoming increasingly powerful. The level of, I mean the kind of work that you can do to actually validate endpoints in those databases, that work is being done now. Those are becoming probably more and more reliable endpoints for making registrational policies. That's in pretty stark contradistinction to what we can do right now in many times in global health settings where there are a lot of methodological problems with many clusters, in my studies for example, and some of those data are really, really uninterpretable and there's a lot of, you're always going to be subject to uncertainties around the assumptions you make in designing some of these studies. But I think that it really does speak to the need to have extremely robust partners and players in that space. For us as an upstream developer, we absolutely are as eager as you to see very robust

capabilities being developed for global health applications in that real-world space. I mean, I think the exciting thing about vaccines, of course, is you can also look at herd immunity and other things that actually may give you, show an unexpected upside to your vaccine perhaps beyond what you can look at in a phase III study, but we still have a lot of challenges before we can be at any, you know, follow the lead of the oncology field.

MR. CAVALERI: Maybe to add that, I think this is very important and in Europe, we started, you know, asking systemically for all influenza vaccine to collect effectiveness data which, and there is again a project which is partially funded by the European Union that is trying to help in doing that, and it's really challenging because indeed the vaccines are used unpredictably across the different member states over the years, so you never know which vaccine will be using which countries and for which, you know, target population, which makes it extremely complex but also stress the importance of setting up good networks that can run these trials, and the importance of, you know, since in most of these cases these are a secondary data collection, so how to have the databases talking to each other and being able to merge data set from different countries and maybe regions in order to have the power that you need in order to determine the effectiveness. All these are huge problems but I think there is a need to do more and we are pushing a law that this happens in Europe first of all, but also in other parts of the world in low and middle income countries, there are a number of vaccines that will be used mainly there, and in many of these countries, that is not even a pharmaco-regional system to begin with. So there is not even, you know, basic surveillance system to report adverse drug reaction. So we really need to put in place capacity and to build the structure that is able to conduct these studies rapidly, both to inform on safety and effectiveness of vaccine, but also for basic surveillance. We need to understand how diseases are circulating, how pathogens are circulating. So this is really a big area that deserves more work.

MR. KASLOW: So in the low and middle income countries, obviously there's huge infrastructure gaps, and in fact for a very large implementation trial program, the more a vaccine is,

there wasn't even a baseline data to start the study, so we had to run an epidemiologic baseline study even to start the implementation program. So there, but I think the good news is a couple fold. One is a pretty strong move away from vertical types of healthcare programs to more horizontal ones, moving towards primary healthcare so we can capture a lot more data across a lot more disease areas than we would if we were stuck in this kind of vertically oriented world. I think the other hopefully good news is a real push to incorporating digital and electronic health records in that system and hopefully we can do in low and middle income countries for health what happened in telecommunications, which is skip land lines, go right to smart phones. And that's actually what's happened and if we I think can help drive that and there's an incentive, added incentives for doing that, it could set us up in a pretty good place. We're doing real-life evidence based trials, but we've got a way to go.

PUBLIC QUESTION: I would like to make one short comment a little off the biomarkers but coming back to the efficacy trial discussion. So one of the big hurdles of doing efficacy trial for only those incidents, but for diseases like Chikungunya when you have smaller pricks, a big hurdle is regulatory pathways in additional authority so transmissions, then really, it can be really slow and the processes can be slow, and these can really prevent getting trials and there is a huge lack of harmonization between countries. Even in Europe there is harmonization and this is a big problem.

PUBLIC QUESTION: I want to reply to Jeff's call for discussion of real-world evidence, and again that's really, that's the space that he works in. We're not in the pre-licensure space very much at all, somewhat but not very much, and I think that there's a great opportunity for efficiencies in building the systems on existing public health surveillance systems that are already set up working with health departments at the state and local level, working with healthcare facilities connected with providers, increasingly developing the tools to use electronic health records and other sorts of administrative data from healthcare to be able to address some of these questions. So I would really hate to see kind of separate systems built where there's the possibility to build on existing systems to answer some of these questions.

MR. ROBERTS: Yes, that's absolutely right. I think there's also kind of potentially untapped synergism here where the CDC would be involved earlier in the discussions about how to confirm clinical benefit, which might lead to less of a lag time to the recommendations being made. They are, understand better what the vaccine is that's being developed and how well they work and a part of designing the trial to confirm clinical benefit, there could be some synergism there. I wonder if you could comment on that.

PUBLIC QUESTION: Yes, I think that we have examples where that has worked better. For instance, I think, you know, we've worked with BARDA on certain vaccines or products where I think we've, for instance, this actually isn't BARDA but our involvement in Zika from the very start I think was beneficial to CDC and I certainly hope was beneficial to the larger community that is developing vaccines, and I think, I feel like maybe there's more of an awareness of the need for those sorts of discussions and points of sort of contact and, you know, information exchange now than perhaps there was in the past, but I think that there's a lot of room for continued growth. At the very least in terms of involving public health authorities, and I'm not talking only about CDC, I mean I think this applies across the world, in discussion about what those sort of post-licensures confirmatory studies might look like. What already exists that could be used as a platform. I think there's, you know, potential for a lot of synergies there.

MS. ARTHUR: Can I add to that, I think that one of the other things building it on the rate to the idea of building on the current public health infrastructure, I think the other thing it would help with is valuation of the vaccine impact because I think particularly as we start to look at treating adults and seniors, you're losing some of the important data about the involvement of infectious diseases in the overall, in the outcome, you know. So a person is in the hospital, they might have pneumonia, they die of something and on the death certificate it says cardiovascular disease as opposed to pneumonia. So how are we doing in capturing all the different incidences and role of infectious diseases in driving worse outcomes of patients with underlying chronic disease? Doing a better job of

documenting these kinds of things would actually help with the valuation and overall outcomes look. And I think the work that BARDA did through drive on sepsis is a great example of just really differentiating some of the impact of these things so it's not just being captured in some catch-all. That's real-world evidence that I think would be very important for infectious diseases long term.

PUBLIC QUESTION: The death certificate data is a great example of something that is, there's just way more information easily available now through electronic health records and other sorts of data, and it also provides a platform in which additional testing can be inserted if needed. So things like pneumococcal serotype-specific urine antigen detection to pneumococcal pneumonias that might not be bacteremic and might not otherwise be captured. If you have a platform in which that can be laid in and a public health system that's capturing the data that comes out, then that's probably good for everyone.

DR. MEHRING LE DOARE: I just wanted to ask a question about the biomarkers. So they are not vaccines, there are now these consortia looking at which web across industry and an account of the CDC is trying to identify these biomarkers, but the consortium is still reliant on a manufacturer taking that forward to get the vaccine licensed, and that majority impacts on low and middle income countries where there's much less of a market for that vaccine, and I wondered whether the panel could suggest some ways to keep the momentum going.

MR. KAUFMAN: I think it's just really important to spend the time collecting the information that really establishes the compelling value proposition for that tool, and I don't think we do that as well as we should in the nonprofit sector as compared to the commercial sector. Because in the commercial sector, before we started a research project, we were pretty sure there was a compelling value proposition. And we haven't necessarily done that that well in the nonprofit sector, and so one of the things that the WHO is working on through the product development vaccine advisory committee is really sitting down and saying, so what are the key elements of a full public value of vaccines? How do they really fit into the whole infrastructure? And what's the value, not just to the

ministry of health, but what's the value to the ministry of finance and business and other folks, and I think we probably need to invest a little bit more there and also establish what's the value of this vaccine beyond the direct immediate health benefit? That population-based health benefit but also the social and economic benefit. This is not something that we've really, we haven't matured tools for doing that, but I think it's in everyone's best interest that we do that and invest in doing that, and so there's some work that's going on in that regard.

PUBLIC QUESTION: I think my question or comment has something to do, this meeting I think we organized this meeting in part because we want to lower the bar to get vaccines into public use where they can do some good. And so the question is if we really want to try to achieve the connecting genomics to oncology treatments and getting personalized medicine type of grant to vaccine development and being able to use these platform technologies and have interchangeable antigens and things like that. We need more information, so if Marco collects effectiveness data when we are using crude vaccines and ELISA endpoints, we are never going to really understand how those vaccines are working. And so I guess the comment or question is, because if we are trading out, like the record indicated for trading out antigens into platform technologies and the antigens are not really very good, it's not going to help to have a fantastic new platform for delivery. So the question is if there is a benefit to getting post-marketing, to do a lot of this efficacy testing post-marketing, could there be a set aside of tax on that post-marketing licensure trial to do more specific sample collection and more detailed immunological assays and trying to apply some of that post-marketing benefit back to understanding community and pathogenesis, and that way we can collect samples. Now if you're doing a thirty thousand person post-marketing study but you set aside two hundred of those people to do intensive sample collection, maybe then we could start getting atomic level antigen designs right and get the immune response measurements and cell repertoire right in the next product.

MR. CAVALERI: That's a valid point and I think indeed, you know, in some of the post residual measures that will finish not just collecting effectiveness per se but there is a need to do

something else, to do something, you know, more elaborate or customized depending on what is the research question there that we need to answer, but I think also in the network for effectiveness in Europe of course we, in some of them at least there is clearly also some additional virology that is being introduced because we need to understand what is happening also on that side. It's not just collecting secondary data from a database and that's it. We need to learn more, so I can only agree with you that it would be good to try to figure out what else can be done with respect to how to handle then in terms of fees and so on. That's a more complicated topic I guess.

DR. GRUBER: I mean, I couldn't agree more. The question that I have, who's going to do it and who's going to finance it and who's, because again, if you ask the regulator, if I approve a product, I deem it safe and effective, and in the post-marketing era, I can only require something or, you know, I only have authority to require additional trial if I have identified a safety signal or if I licensed something based on an accelerated approval so that I can require a post-marketing study or if, you know, there's some provisions all to do the pediatric research equity where I can require something. But I could never ask a vaccine manufacturer okay in your post-marketing study that you will be doing. You're going to now sample X number of people and do serology or O-mix or whatever I would like for them to do, so I think there is again a discussion here that, and I also don't think that the burden can only be on the vaccine manufacturer. There is something sort of the greater community and different stakeholders have to come together to really discuss it and make this happen, because this is something which I think would be great, but this is nothing that we can require, you know, as a condition for approval.

MR. CAVALERI: Yes, I will just additionally allow more flexibility on what we can require if there is a need in terms of risk management plan and other commitment post authorization but I would agree that indeed one of the big issues here is how to put together requirements to manufacturers versus what the public health authorities are doing and make them collaborate together, which at least in Europe has been really an issue. The issue is that there are some public health

authorities that, you know, they cannot really even work with industry, so there is really a barrier there and how to put this together and make it happen in a way that the manufacturer will have the data that they need in order to fulfill their requirements and the public authorities will have the data they need to understand the impact of their vaccination campaign is not straightforward and that's why we are trying in Europe to create some finial level that would allow a more transparent communication and working together between the public authorities industry and bodies like DMA so that to make sure that the data that we all need even for different purposes will be there. But it's a bit of a journey, I have to say.

MR. KASLOW: Actually, let me just, going into dangerous territory here, but just to pick up on your point is using biomarkers as the basis of licensure and then with a strategy of then proving effectiveness post-licensure can work in high income countries. In the low and middle income countries I think we need to be really transparent about that strategy and where the risk and the cost are being shifted to. And in many cases, that's going to be going to the countries and not necessarily a manufacturer, so I think we just need to be, and that may be the right answer, but I just think we need to be transparent and understand exactly what the dynamics are there and be prepared to manage those, because I think that in part is what's happening and that's going to require a pretty substantial investment from the government or the public I order to have the infrastructures to actually to be able to use that strategy in low and middle income countries. And that may be the right thing to do, but we should be really transparent about it.

DR. GRUBER: Thank you for that comment. I think we're going to take one more comment.

PUBLIC QUESTION: Yes, I think that's just in line with what we just requested in terms of collecting those samples. I am obviously biased coming from an epidemic background and just wanting to look into multiple samples, but what's happening right now in the influenza field is that a lot of companies are going to go into clinical trial soon and they're not going to make the products and the adjuvants available to other companies or institutions to decide that person and they're not going to

share samples. And I think we're losing a lot of information that way by not being able to do those comparisons. And I'm thinking BARDA did something with the stock pile for adjuvants and antigens where they are able to mix and match in a way that companies and other institutions can't do it. Is there any way for trials that have some public involvement to maybe have a requirement to set aside a certain set of samples that doesn't have to be analyzed by the company itself but can be made available to epidemic institutions to just do certain testings in a side-by-side way?

MR. DISBROW: Maybe. So it's a difficult question. I mean, so the mix and match study was done during the, you know, heat of the pandemic and so we needed all the companies to work together and so we have specific legislation that allowed us to do that. But the trials when they're being run by the sponsor, I mean there is commercial confidential information in those samples and that's where it becomes very difficult to share those with other people, and a lot of people, you know, have indicated at multiple meetings, well, it's sponsored by the federal government so therefore people should have access to those samples; and that's partly true. I mean, most of what we do is a cost share. It's not always one hundred percent supported by the government, so it makes it really difficult to, you know, make those samples accessible. So not trying to dodge your question but it's very, very complicated. We do studies, like we did the Bright study where we took ten-year-old adjuvant that had been, sorry, antigen that had been stored in the stockpile, we ran it. We might be able to share those samples with you because that was a BARDA-sponsored trial, but when it's a trial that's sponsored by a specific company, that's much more difficult.

DR. GRUBER: So I'm looking at the clock and I see people walking out because I think we are a little bit above time. I just wanted to really take the opportunity again to thank all participants of this workshop, all the speakers, the panel members, but also in particular the audience for the many good comments and questions and stimulating thoughts. So I very much appreciate you all coming and I think we have some work to do to try to capture all these perspectives in the meeting report that we decided we're going to write, and so from my perspective, really, thank you very much. I

hope you also found this workshop informative, and I just wanted to turn it over to my colleagues and co-organizers to see if they wanted to have some parting words.

MR. ROBERTS: Just to enter the repeated question that we've had about whether these presentations will be made available, and again, we're going to send an email to the presenters and beseech you to make your presentation available, even if you have to remove some of the slides because I think it would be very helpful for everyone to have access to those. And the other thing is that I think we will try to make available on the registration site a version of this survey that we did so that we can continue to make that available if anyone wants to weigh in on those questions up until we submit whatever this paper is, will integrate these perspectives to the best of our ability and to this meeting of course so we will try to make those things happen in the next few days so be on the lookout for that.

DR. GRUBER: Thank you very much. And so I just don't want to adjourn the meeting before I forget to thank, and I thanked them yesterday, but I need to thank them again, all the people who are responsible for the logistics. And I see the lady sitting here to the right, you know, paying attention, transcribing, and I think there's Monica in the back. I mean really, people outside probably that are not in the room, but there has been so many people involved to really guarantee that this workshop is running smoothly. And I think, you know, they did a marvelous job to contributing to the success thereof, so thank you again to all these people, and I can't name them all because I don't want to because I will forget one or two and I want to prevent that, but thank you. Thank you again to all the support stuff. Okay, and Monica, you're going to get a shout out. So I think the meeting, the workshop is adjourned. Thank you.

(WHEREUPON, the Scientific Meeting was adjourned at 3:05 p.m.)