MONOCLONAL ANTIBODY PRODUCT DEVELOPMENT FOR RABIES

POST-EXPOSURE PROPHYLAXIS

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P R O C E E D I N G S

DR. COX: First of all, I wanted to just welcome everybody today to -- joining us for our workshop on developing rabies monoclonal antibody products as a component of rabies post-exposure prophylaxis. And just to start out with some nuts and bolts, important issues, as far as lunch, I've been told to let you know that there's a kiosk that's right across from the registration desk and if you -- you know, over the course of the morning and -- Sunita, how soon should they go out to order? So, any time this morning, but probably, you know, by the break. If you order your lunch at the kiosk, that will prevent some of the delays that can happen when everybody sort of descends on the window out there to get lunch. So, just want to take care of that nuts and bolts issue, it's important. And I think, you know, over the course of the day, we'll hear a number of important talks about the epidemiology of rabies, we'll hear some about prior approvals for H (Inaudible) rabies immunoglobulin, the type of evidence that was

available, what can be learned from pre-clinical and some of the available clinical data from previous products that have been studied for treatment of prophylaxis, I should say prophylaxis of rabies. And as we'll discuss today, developing a new monoclonal antibody for post-exposure prophylaxis of rabies carries with it a number of challenges, and we found workshops as these to be particularly helpful as we work through challenging areas of drug development and clinical evaluation of products. And there are certain characteristics, if we reflect upon rabies, you know, what makes this difficult? Why is this challenging? And it is interesting, if you look across other areas that are difficult and challenging, and this may be even more challenging than some others, there are certain characteristics of the disease and the available therapies that make this difficult. There's a tremendous urgency to initiate treatment, in this case, early post-exposure prophylaxis, in the setting of a suspected case. And for each

individual case, there's a degree of uncertainty as to the level of risk for the particular exposure, but you know, with rabies you need to err on the side of treatment to avoid missing an opportunity to administer a lifesaving post-exposure prophylaxis regimen. The available preventative measures work quite well, in -- you know, for many, so we don't want to lose efficacy, given, you know, the consequences of a reduction in efficacy for a disease such as rabies, then there really is no realistic opportunity for rescue therapy. You know, what needs to happen needs to be effective and needs to be given urgently. And also, making this challenging, too, that the regimen is really -- there are multiple components, each of which adds something to treatment or to post-exposure prophylaxis. You'll probably catch me saying that over the course of the day, treatment, when I really do, in fact, mean post-exposure prophylaxis, which makes it difficult to quantitate the contribution of each of the different components, you know, overall in

the treatment regimen. And I'm sure as the day goes on, I'll learn more and we'll talk about other factors that we need to think about in developing and characterizing a new product for post-exposure prophylaxis for rabies. As part of our discussions, too, it will be important, as we work through each of the different components, what can be done to think about the value and limitations of the information that can be gained, and if there are limitations, is there additional information or research that could help to close some of these gaps? A question that we'll talk about, I'm sure, is how much evidence is needed before relying upon a new monoclonal antibody for post-exposure prophylaxis as part of an overall regimen? How much do we need to know? What level of evidence do you need to have before relying upon it in people who've been exposed? We should also keep in mind that there are risks that make one nervous as you think about a clinical trial. You know, what are the -- you know, what are the reasons that, you know, there's trepidation when

entering into a clinical trial. And if you reflect on that for a moment longer, you see that, in fact, the clinical trial is probably the most controlled setting. So, those -- although those trepidations and nervousness may be somewhat more removed, they are only amplified in the setting of use outside of a monitored setting, such as a controlled clinical trial. So, I hope and expect that we'll find that the type of information that we, as regulators, want is really the same type of information that scientists and patients and we all -- and clinicians, essentially, which we all are, too, I think we all sort of overlap in our disciplines and our perspectives, it's really all the same information. And that really is, you know, will the product be effective in post-exposure prophylaxis for patients exposed to rabies? So, we'll work towards, you know, understanding what information can be gleaned, the limitations of that information, and what additional work might help to further close the gaps out there in knowledge. For diseases like

this, they are particularly challenging. Oftentimes, those challenges and frustrations really arise from the biology of the disease and the limitations of our knowledge. So, we'll continue to persevere and work through it and get to some answers, solutions, and identify the limitations of what we do know. So, with that, I want to -- and one other thing, too, on that same theme, is that we really can't change the biology of rabies disease, at least not yet. So, really, our position is one of trying to understand it best, so that we can study it well. So, I look forward to today's discussions and towards our shared goal of figuring out our approaches for the development, evaluation of new monoclonal antibody products as a component of rabies post-exposure prophylaxis to meet patient needs that are out there. So, thank you, and at this point, I'll turn the podium over to Sarah Connelly.

DR. CONNELLY: Good morning, everyone. I want to echo Dr. Cox's welcome today to all of our speakers, panellists, and participants, and I have

the privilege of presenting the opening talk to set the stage for what I hope to be a productive and valuable workshop on this important topic. Now, the first order of business -- let's see if I can advance the slides. Okay, I can. The objective of today's workshop is to discuss the challenges and identify additional scientific work needed to advance development of monoclonal antibodies targeting rabies virus for use in a post-exposure prophylaxis regimen to be used in conjunction with licensed rabies vaccine. This public workshop is being held to facilitate sharing of the available data and the complexities in the field of rabies post-exposure prophylaxis. It is not an advisory committee, decisional meeting, or regulatory meeting on any specific product or products. Rather, today's meeting is intended to be a forum for discussion and for identifying research gaps regulatory -- to both regulatory and public health issues. Infection with rabies virus results in a fatal encephalitis. There is no established current treatment

available to treat rabies infection once symptoms appear, and survival is rare. Approximately, 55,000 rabies deaths occur each year, with most occurring in Asia, Africa, and Latin America. Public health efforts are directed toward prevention strategies, including animal vaccination strategies, particularly in the dog population, pre-exposure prophylaxis for those at increased risk of contracting rabies, such as veterinarians, which consists of rabies vaccination with periodic boosters, and post-exposure prophylaxis for high risk exposures, which are recommended to consist of either a rabies vaccine and immunoglobulin regimen for those without prior rabies vaccination, or rabies vaccine booster regimen for those with prior rabies vaccination. Approximately, 11 to 36,000 people receive post-exposure prophylaxis annually in the United States, and more than 15 million people receive some form of post-exposure prophylaxis annually throughout the world. Today's workshop focuses on post-exposure

prophylaxis, and you'll hear several talks highlighting important information to contribute to the subsequent panel discussions. Dr. Taylor will provide background information on rabies epidemiology and vectors, and this slide from the WHO illustrates the global scope of rabies, with the darker green areas indicating high risk areas of humans contracting rabies. The United States is categorized as a lower risk area by the lighter green colour, though it is not classified as a no-risk area. Here are a number of animals known to transmit rabies virus to humans. In the United States, bats and wild animals, such as raccoons, fox, and skunks are the more common vectors, whereas globally, dogs are the predominant vector. And let me see if I can use a pointer -- I guess I'll use this screen. Once a person is bitten by an animal harbouring rabies virus, the virus replicates in the muscle and, after a certain period, will travel in peripheral nerves to the central nervous system, which ultimately results in a fatal encephalitis. This schematic graph

illustrates the dynamics of rabies virus pathogenesis. After the virus enters the tissues, there is a variable incubation phase, ranging from days to years, and after that phase, it spreads to the peripheral nerves to the central nervous system, which ultimately results in a fatal encephalitis. And so, the role of post-exposure prophylaxis is to act here and neutralize the rabies virus. The CDC advisory committee on immunization practices and the WHO recommend post-exposure prophylaxis for the circumstances listed on this slide. ACIP recommendations are by animal type and WHO by the category of exposure. And I want to particularly highlight Category III exposures, which are single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membranes with saliva, or contacts with bats. Post-exposure prophylaxis should begin as soon as possible, though there is no time limitation beyond which use of post-exposure prophylaxis is not recommended. The recommended regimens for

suspected rabid animal exposures for ACIP and WHO Category III exposures are outlined in the below table, and I want to point out that these recommendations pertain to those who have never received prior rabies vaccination. For persons who have received prior rabies vaccination, boosters at day three -- sorry, day zero and day three are recommended. The essential post-exposure prophylaxis elements -- could we get the pointer -- consist of extensive wounds cleansing and administration of rabies immunoglobulin, day zero, in and around the wound, with any remaining dose administered intramuscularly. The ACIP recommends human rabies immunoglobulin, while the WHO recommends either human rabies immunoglobulin or equine rabies immunoglobulin. And the third component is rabies vaccine administered either intramuscularly or intradermally, depending on ACIP or WHO recommendations. And in cases when there is a delay in administering rabies immunoglobulin, it is not recommended to administer it beyond seven days after receiving

rabies vaccine to avoid rabies immunoglobulin interference with the active immune response. Now, this schematic graph shows the vaccine-induced humoral immune response, which becomes detectable approximately seven to ten days as shown in the solid blue line after the initial vaccination. I want to highlight this window period shown in the red arrow between the time rabies virus is introduced into the tissues and the vaccine-induced immune response becomes detectable. And it is in this window period that rabies immunoglobulin, or any other passive immunization, is intended to provide protection. The current US-approved rabies immunoglobulin products are HyperRAB and Imogam. As stated in the HyperRAB label, the usefulness of prophylactic rabies antibody in preventing rabies in humans when administered immediately after exposure was dramatically demonstrated in a group of persons bitten by a rabid wolf in Iran. And in the Imogam label, it states that controlled clinical trials of human rabies immunoglobulin have not been

performed, however, extensive field experience from many areas of the world indicates that post-exposure prophylaxis, combining local wound treatment, local infiltration of rabies immunoglobulin, and vaccination is uniformly effective when appropriately administered. And Dr. Scott will provide more details on the data supporting their approvals, which will contribute to today's discussions. Available approved and licensed rabies vaccine and rabies immunoglobulin are considered highly effective at preventing a highly lethal disease. However, there are global challenges to utilization of and access to the recommended complete post-exposure prophylaxis regimen components, including supply, cost, and storage considerations, and Dr. Wilde's talk will provide an informative global perspective on the use of rabies post-exposure prophylaxis. The WHO expert consultation on rabies report from 2013 includes a statement that more research development and assessment are needed of suitable immunoglobulins or alternatives, such as human

monoclonal antibodies in rabies prophylaxis to ensure wider access to passive immunization at a reduced cost. We'll have the opportunity to hear WHO industry and academic perspectives on their experiences with rabies monoclonal antibody development to contribute to today's panel discussions. Assessing the activity of a novel rabies product, including a novel rabies monoclonal antibody as a component of the post-exposure prophylaxis regimen is critical, and we'll have talks providing perspectives on the use of animal models by Dr. Ellison, the use of serologic assays by Dr. Moore, and the use of clinical trials by Dr. Bell and Dr. Valappil. Regarding animal models and cell culture, some of the issues in assessing the activity of a rabies monoclonal antibody as a component of the post-exposure prophylaxis regimen include the breadth of coverage against diverse rabies virus strains and selection of monoclonal antibody dosing regimens for initial clinical evaluations. Regarding serologic assays, issues include the use

of these measurements in understanding passive protection during the first few days of post-exposure prophylaxis, and in understanding the effects of novel rabies monoclonal antibody products on rabies vaccine response. Clinical trials of monoclonal antibodies may be generally categorized as those conducted in the non-rabies exposed population and those conducted in people with a suspected rabies exposure, and I'll focus more on clinical trials in the next few slides. From these talks, and in these panel discussions, we look forward to a dialogue about what can be learned from these assessments and what are the uncertainties in research gaps. This slide focuses on clinical trials conducted in the non-rabies exposed population, which allow the study of different components and combined regimens of established and proposed post-exposure prophylaxis in non-rabies exposed healthy volunteers. Initial exploration of tolerability and information about a novel rabies monoclonal antibody adverse event profile may be learned from these types of trials.

Furthermore, clinical trials in this population allow for monoclonal antibody dose exploration to examine questions, such as can higher doses be identified as excessively interfering with active response to vaccine? Can lower doses be identified as unlikely to provide adequate protection during the earliest time period before protective vaccine response begins to be established? And during today's workshop, we encourage discussion about the question, what evidence is available to support predictions from serologic assay parameters to inform expectations of protection in the rabies exposure setting? Regarding clinical trials with rabies monoclonal antibody in the suspected rabies exposed population, an important question is, what is the best achievable understanding from clinical trials, that a novel rabies monoclonal antibody product provides protection from developing a lethal disease? This question is important, not only because of statutory regulatory needs for evidence supporting efficacy, but also important

for public health and clinical decision making. Hypothetical trial designs, including superiority, non-inferiority, and other possible trial designs and considerations of trial end points, including mortality and other end points, such as serology, will be presented to invite discussion on studying and interpreting the contribution of rabies monoclonal antibody to the post-exposure prophylaxis regimen. There are challenges in assessing passive antibody contribution to the post-exposure prophylaxis regimen. Multiple factors affect the risk of developing rabies after a suspected exposure, such as, was the biting animal rabid? Was the animal shedding rabies virus? How close is the bite to the nervous system? Could the bite site be promptly identified and thoroughly cleaned? Is appropriate rabies vaccination series initiated and completed, and is passive antibody delivered appropriately? The objective of effective post-exposure prophylaxis is to decrease the risk of developing rabies, but the effect of any one factor on this

risk, including rabies monoclonal antibody, may be hard to measure in any feasible clinical trial, as Dr. Cox mentioned earlier, and possibly even harder to accurately deduce from less controlled use and experience. Dr. Taylor's talk this afternoon will provide perspective on the questions of what are important ethical considerations when designing clinical trials of a rabies monoclonal antibody based post-exposure prophylaxis product as an alternative to available hyperimmunoglobulins, and what are ethical considerations for enrolment of children in rabies monoclonal antibody clinical trials? This slide presents examples of questions to keep in mind as you listen to today's talks. What can be learned from animal data, serologic data, WHO industry and academic experiences, and from clinical trials? What is the nature and strength of data supporting direct links between any specific in vitro animal or serologic assessments and the contribution of a specific component and dose of post-exposure prophylaxis to human clinical outcomes? What are

the research gaps in understanding the contribution of rabies monoclonal antibody to the post-exposure prophylaxis regimen? What are potential uses and limitations of possible clinical trial designs? And what are ethical considerations in rabies monoclonal antibody trial designs? These are just some of the possible questions that we hope will be discussed throughout the day to aid in identifying research gaps and uncertainties in this important area. And I'll conclude my talk with a quote from the French essayist, Joseph Joubert, who wrote that, "It is better to debate a question without settling it than to settle a question without debating it". We may not be able to answer all the questions that come up today and, in fact, it is possible more questions may be raised as a result of the discussions, but it is the nature of the discussion, and the nature of identifying what are the research gaps and uncertainties relevant to regulatory and public health issues that will be extremely valuable in advancing rabies

monoclonal antibody development? So, I thank you very much for your attention, and I now would like to introduce our first speaker, Dr. Louise Taylor, who we are thrilled was able to come join us today. Dr. Taylor is a research biologist who has worked for the Global Alliance for Rabies Control, a non-profit dedicated to reducing the burden of rabies in humans and animals, and she's worked there for over ten years. She coordinates their international technical expert group, the Partners for Rabies Prevention, contributing to the many technical -- many of their technical tools and scientific papers, and is involved in the GARC communications to the rabies community. So, very much looking forward to her talk, and I will turn the podium over to you.

DR. TAYLOR: Well, thank you to the organizers for my invitation to speak today and to be part of this very important discussion. I have been given a very wide topic area, a global perspective on rabies in animals and people, about the different vectors, and about the different

rabies strains. So, what I'm trying to do is instead of going into huge amounts of detail, is give an overview of, I think, what will be most relevant for the discussions that come. So, to put rabies virus in context to start with, rabies virus is there marked by the red star. It's one of 14 different species in the Lyssavirus genus. Many of these have only been recently classified into that genus and there are more under consideration. So, we are really still learning about this group of viruses. What we know about most of them is that we understand the reservoir is in bats and so it appears that this whole group of viruses have co-evolved with bat species over millennia. Several of these species have also been noted to cause human infections, but with the exception of rabies, these are very occasional infections. It is not a very large public health threat apart from the rabies virus itself. So, I've written on the right-hand side there the viruses which have been found to cause human infections. Those infections are very rabies-

like, they are transmitted by bites or scratches. Most of these have been directly transmitted from bats, but rabies virus is the one that causes the largest public health threat with the latest estimation being around about 59,000 deaths per year. I also highlighted in this table with blue stars those of the species which are in phylogroups 2 and 3. These are the ones that are genetically most distinct from the group that contains the rabies virus. And I mention those just because those are the ones where our current post-exposure prophylaxis for rabies virus is not expected to be effective. Not all of those have been noted in humans, but if it is, then we are without post-exposure prophylaxis for those species. So, rabies can be quite a complicated epidemiology to understand and in different settings, we have different species involved. Theoretically, the rabies virus can infect any mammal, which makes it sound horribly complicated, but to understand it best, we can divide those hosts into three different groups, really. There

are reservoir hosts, and these are the ones that transmit the rabies indefinitely. So, the virus is maintained in these reservoir hosts and it over time becomes adapted to those hosts. So, when we talk about different rabies variants, these are because they have become adapted to those particular hosts in which they persist. So, although all mammals can be infected with rabies, the reservoir hosts come from two groups, the original bat hosts and then a group of carnivores which seem to be the most adapted to maintaining this. From those reservoir hosts, we can have infections in a large number of mammals which we call spillover hosts, and those can be both wild animals and domestic animals. We may even have short chains of transmission, as indicated by that little pink arrow there. There may be short chains of transmission, but the rabies virus is not maintained within those hosts for any length of time. Now, in terms of human exposures and the public health risk, humans can be infected by any of these hosts either a reservoir host or a

spillover host. Both of those can act as infectors to transmit the virus to humans. And what makes the difference really in assessing the public health threat is two things, one is whether the animal that was biting the person was a reservoir host, in which case it's more likely perhaps to have the rabies virus, and also the contact rates between humans and those different animals. So, when we look across the globe, by far the biggest public health threat is from the domestic dog. The WHO estimates that more than 99 percent of all human cases of rabies result from dog bites. So, dogs are a very good reservoir host, it's been evolving in dogs a very long time, and humans live very closely associated to their dogs and those two things combined make that a very high public health risk. This is the most recent WHO canine rabies risk map, this was put together at the start of 2016, and you can see all these countries in blue have endemic dog-transmitted human rabies, so the dog-transmitted rabies is affecting large numbers of people, it's

uncontrolled largely in the dog population. So, Africa and Asia are still battling with extremely high levels of dog-transmitted rabies. Latin America is of significance because over the last 30 years, and I'll show you a graph of this in a moment, they have had enormous impact on the amount of dog-transmitted rabies and now we only see endemic dog-transmitted rabies in a very small number of hotspots across that whole continent. North America and Western Europe eliminated human rabies from canines -- sorry, they eliminated canine rabies in the last century, and Australia was always historically free of terrestrial rabies. What does this mean in terms of numbers? Well, this is the most recent estimates we have for canine rabies, the largest public health threat, and I will say although a lot of data and a lot of collaboration went into the study, this was published by Hampson et al in 2015. There is also a lot of extrapolations, so these are estimates with very wide (Inaudible), but our estimates as best we can guess them are around

about 59,000 people a year die, all -- almost all in Africa and Asia, so 21,500 deaths in Africa, over 27,000 estimated for Asia. There is extremely low numbers in Europe where canine rabies is largely being controlled and across the Americas, and of those 182 at that time, there was a large proportion of those in just one country, in Haiti. So, in terms of exposures to rabid animals, this was estimated by looking at the dog population sizes and the probability that those dogs are vaccinated, and these are estimated that across the globe, across these 122 countries where canine rabies is endemic, there were 15.7 million exposures to rabid animals. In terms of estimations, and these are very difficult to estimate, but PEP is delivered worldwide and the study were estimated at over 29 million. There are certainly reports from countries like China that over 15 million PEPs are delivered every year there. Asia is extremely high usage of PEP and in fact, PEP availability in Asia is much, much higher than in the other regions where dog rabies

is a problem, particularly in Africa where we see a lot of PEP shortages. There is no doubt that this PEP is saving lives and the model estimated about 2.9 million lives were saved by this PEP delivered each year. So, the largest public health threat is from dog-transmitted rabies globally. What about other sources? And I wanted to show you this data, this is from the whole of Latin America over the last 30 years. The human cases from dogs there in red have fallen very, very dramatically as the cases in dogs which are shown in blue here have fallen. This extensive mass dog vaccination has reduced that to almost elimination. But as those cases have come down in humans, what we've noticed is this line in green at the bottom, these are human cases transmitted from vampire bat. And often what we find is that it's only when the dog-transmitted rabies disappears from a country that you start to notice there are sources coming from wildlife. But even after some of these years where we've had quite significant outbreaks of vampire bat-transmitted

rabies, there number of cases in humans still don't reach anything like the numbers of cases we had when canine rabies was highly endemic in these countries. Turning to the US now, in countries where we have extremely good surveillance, where we sit right now, we have a very good idea of which species are transmitting and maintaining rabies in which area. And so, this is the map from 2015 from the CDC, people in the room who know this work much, much better than I do, but we are able to define very clearly where the edges of these reservoirs of rabies are. And in each of these areas there are genetically distinct variants of the rabies virus and we can type those strains, I'll show you some data in the next slide, and suggest, even if the animal is not a reservoir species, exactly where it has originated. So, in 2015 over five and a half thousand rabies-positive animals were found in the United States by very intense surveillance efforts and over a quarter of those were typed. So, we can look at the different variants and look at the

animals that were found and that tells us a few different things. The blue circles here show you that the vast majority of cases in raccoons are a raccoon-adapted strain of the rabies virus. Again, in skunks, the vast majority of skunk cases are a skunk-adapted strain. And again, in bats, all the cases that were found in bats in 2015 were of a bat virus as you would expect. Now, for the terrestrial wildlife hosts, there is evidence of spillover and so raccoons may transmit -- may be carrying the skunk variant and vice versa and when we look at domestic animals, we see that a large number of these different strains can pop up in our domestic animals. This is the spillover effect I showed you in that diagram earlier. In terms of public health threats, we need to look at how frequent it is for people to come in contact with these different animals and so raccoons and skunks, which have become adapted to city environments in many cases, can become quite a public health threat even though they are a wildlife species. But if these virus variants get

into something like dogs or horses, cattle where there's much more contact with humans then they can be -- even though there's a small number of cases, can be a more significant public health threat. The dog's cases that were found here, none of them were the dog rabies variant which was confirmed eliminated in 2007. And in 2015, the only human case that was acquired in the United States originated from a bat. This is the most common cause of human deaths in the United States largely because people don't notice that they've been bitten by a bat. It may occur at night when they were asleep. We have similarly very good data from Europe and I've looked here to the rabies bulletin Europe database, you can search this online, and I just pulled up for the years that I chose, terrestrial wildlife cases. These are largely in the red fox species and you can see those have been pushed to the eastern part of Europe. These was endemic all over western Europe, but a very, very large scale rabies vaccination program has pushed that back and

they're now confined really to the east part of Europe. The bat cases have a much wider distribution, you see that in red in the center, but the domestic animal cases tend to reflect that of the terrestrial wildlife cases. So, this is evidence of spillover from the red fox population into domestic animals. Across this whole time range, there were only 59 human cases reported from across this area of Europe and 47 of those were from three countries in east Europe. So, what we see as well as in -- similar to the United States is the number of human cases is extremely low. We do understand the reservoirs in these circumstances, we do have good access to post-exposure prophylaxis, and in terms of deaths, the human impact is very low. What about globally? Now, I'm not going to profess this is exactly every single reservoir that has been identified, but these are the key ones. We have well-known rabies reservoirs (Inaudible) wildlife in countries such as the US where this is being well studied, across Europe. We have airborne wildlife

sources from the bats and I just wrote this across the bottom because this has been documented from many different countries, insectivorous bats can be a source of rabies. And then, of course we have the domestic dogs and I just put that in huge letters across Africa and Asia because where we have rabies and domestic dogs, we generally also have very poor control, very poor emphasis on rabies control, and very poor surveillance, so we don't really know what else is going on. We know it's in dogs, we don't know much more than that. There are exceptions to that around South Africa, there's been some work on a number of different wildlife reservoirs, so we have the tools to identify these reservoirs where we have the surveillance capacity to do that. I want to point out on the right-hand side there the ferret-badgers. This was an interesting case because nobody had that on their radar at all until in 2013 in Taiwan, an outbreak was noticed in ferret-badgers. This has not, to date, caused any human cases and the more that this has been looked into,

it's been realized that this infection has been circulating for probably decades. But this went completely under the radar in a country which did have good surveillance partly because our contact rates with ferret-badgers are probably extremely low. So, we can look at the variant types that are associated with these different reservoir species. We can also look genetically and make very fine genetic trees of these different viruses isolated from these different hosts. And we can, where we've got good surveillance, suggest exactly what the origin of that virus was and often quite specifically a location where that virus came from. This is very important for rabies elimination efforts where they want to, at the tail end of controlling canine rabies, make sure that any new cases either came from outside their control area or came from a different species to know that they have had the required effect on the reservoir they were trying to (Inaudible). But in many, many countries, we really don't have good enough surveillance to be sure that every

reservoir species has been identified. I just have a few thoughts on one of my talking points was rabies prevalence in animals. This is extremely hard to pin down because it depends exactly on which animals you're testing. So, just to put some data together from the United States 2015 surveillance, 13 percent of raccoons, 28 percent of skunks, and 6.8 percent of cattle that were tested were found to be rabies positive. Of course, that is not the prevalence in the natural population. These are animals which have been tested either because they're suspected of having rabies or they'd been involved in a biting incident and rabies was to be ruled out. So, we have to think very carefully about this data and how to interpret it. Another study that I found recently looking at wild-caught and apparently healthy bats in the US found 0.6 percent of one species and 2.5 percent of another species were infected with the rabies virus, but when those same researchers looked at grounded bats underneath a very large colony, 92 percent of

those were infected with rabies, so clearly this was an ongoing rabies epidemic in that colony and when you look at that those grounded bats in that particular location, an extremely high number of them have rabies, so that could be a very large public health threat in that particular setting. I just put together some data that I happened to have for dogs tested in the Philippines, 18 percent, 27 percent, 28 percent in different years of the dogs tested were found to be rabies-positive. This is very unhelpful for telling us the prevalence in the natural population, but I would argue that in terms of the public health threat, this is perhaps more relevant information, of the dogs that are biting people, what proportion of those are carrying rabies, how big is the public health threat from animal bite cases. But even so, even just looking at biting animals, they may not be evenly sampled, it may be only telling us a fraction of the picture. So, to try and sum up what else is out there, we know rabies can jump species, it's been well-documented

in the genetics and we know that rabies, having jumped to species, can establish a new reservoir and adapt to that reservoir host. But surveillance in many canine rabies countries particularly is very poor, small numbers of samples are tested, and there are often no ability to test the variant types locally. This is improving and partnerships and reference lab partnerships are helping to support countries and our level of knowledge is increasing for sure on these different variants and reservoirs in different countries. As we saw in Latin America, as dog rabies went down, the wildlife rabies became -- appreciate as a larger public health concern. So, I would argue it's quite possible that dog rabies in many endemic countries is masking a few more wildlife reservoirs. But again, we have to think about the contact rates between humans and those other animals in assessing the public health risk. So, I just wanted to put this last slide here as a bit of (Inaudible) in a way, but we do have two very

different situations in the rabies world. We have a situation like we have in a country like the US where we have a very clear understanding of how hard we've looked for particular virus infections and where we found them. So, in gray here are all the raccoons tested and in red, the ones found positive. If we can very accurately assess what the risk is in these situations, we can use that information to give good advice on when to seek PEP and we also have good access to PEP in countries such as this. So, the two things go together, an emphasis on canine rabies control, historically (Inaudible), and emphasis on good surveillance and good access to PEP. The result is that in the US in 2015 there was only one human death which was resulted from a (Inaudible) exposure. In contrast, in many countries, particularly across Sub-Saharan Africa, we have a situation that's very much clear. We know rabies is in dogs, we presume it's in every -- in all dog populations. We know they have high contact rates with people, we have a lot of dog bite cases, and

we have little idea of other reservoir species. So, the upshot of all this is, really, that all dog bites and often all animal bites need to be treated as a potential rabies exposure. Combining this with generally poor access to post-exposure prophylaxis gives you a very large public health burden and a human case rate of something like 21 and a half thousand each year. So, I just want to leave those two, sort of, images in your mind as we go about these discussions in access to post-exposure prophylaxis and effectivity. I'd like to thank all the people whose work that I've based this presentation on, none of it is mine directly, and I look forward to further discussion. Thank you.

DR. BIRNKRANT: Thank you very much. Our next speaker is Dr. Dorothy Scott. Dr. Scott joined the Center for Biologics in 1993 and has served as the plasma derivatives branch chief since 2003. Her branch is responsible for the licensure of plasma derived immune globulins, antitoxins, and anti-venoms, and performs mission-

related research on safety, potency, and efficacy of these products. Her presentation on the scientific basis for approval of human rabies immune globulin in combination with rabies vaccine will add to the foundation of today's meeting discussion. Dr. Scott.

DR. SCOTT: Good morning. It's a pleasure to give this presentation because I got the chance to research some very old files, particularly the licensure files for the first human rabies immune globulin product from 1974, but that submission contained a large number of old supporting publications and I'm going to tell you a little bit about that. But the reason that I'm giving this talk is because it's important for this group to know the scientific basis for approval of human rabies immune globulin in combination with rabies vaccine. I'm just having a little bit of a technical difficulty. In other words, wrong control, just like at home. Okay, I just need to say that my comments are informal and they don't bind or obligate FDA. The first

polyclonal human rabies immune globulin was licensed in the US in 1974 and that was and is manufactured from source plasma currently collected at US licensed plasma centers, so all these are US donors. The donors are hyperimmunized with US licensed rabies vaccine, the plasma is pooled and purified by fractionation to immunoglobulin. This is licensed for use in combination with rabies vaccine for post-exposure prophylaxis. This is just the schematic for those of you who are not familiar with it, but -- let's see. Very good. The donor's vaccinated, donates plasma, so they're hyperimmunized, that means they received a rabies vaccine much more frequently than you would under a licensed indication. This plasma is pooled from multiple donors, it's fractionated for both products in a very similar fashion using a process developed in the 1940s by Cohn and Oncley, but basically this yields quite a pure immune globulin fraction. The first package insert for HyperRAB, which was that initial product, pretty much sums up the scientific basis

for licensure, interestingly, and there are three points I want to make from this package insert. The first of all is it references as evidence of -- - or supporting evidence for efficacy the Iranian study of rabies immune globulin post-exposure prophylaxis with vaccine, and secondly it references the studies that were done in support of this licensure by the manufacturer, who then was Cutter, now is Grifols. This product is still very much in play and I'll be showing you a little bit of this, but you will be seeing more of both of these studies in other presentations. So, this is an overview. And the third point is that this rabies immune globulin was standardized against a US standard, but that was considered equivalent to the international unit for rabies antibody. And as a matter of fact, that was a standard developed in 19 -- in the early to mid-1950s by WHO, and that standard that was used actually in a paper about this -- the subjects who received equine -- I'm sorry, rabid immune globulin plus vaccine. They used that standard of measure and Cutter used

that standard and measure from the identical standard which was not changed between 1955 and 1974, so there's an actual link between the standard that we have today which is linked to this previous standard that I'll show you, between those Iranian studies and this particular product. So, first, for the Iranian study, I will summarize it, you'll see it several more times, the subjects were victims of a rabid wolf attack in Iran in August, 1954, and these poor folks were shipped to Tehran where they received treatments, and I'm just going to talk about the head wound Category 3 subjects. The vaccine they received was a phenolized rabies-infected sheep brain. That was on a 21 day regimen. They also received a rabbit anti-rabies serum made bilaterally at 0.65 mL per kilo i.m. So, there was not infusion of wounds in these studies. The mortality in subjects with head or neck wounds for vaccine only was three out of five receiving that regimen, and for vaccine with rabbit anti-rabies serum was one in 13. So, you can see there's a drastic reduction in the

number of people who developed rabies if they received the rabbit anti-rabies serum in addition to the vaccine. This was a subsequent paper, but the subjects studied were the same ones that received -- that I just described in the actual study, and this just makes a point that has already been made by Dr. Connelly. And here what we're looking at is days after treatment with anti-serum -- I'll call it rabies anti-serum plus vaccine -- rabies anti-serum plus vaccine and a different dose of anti-serum and vaccine only. And you can see that the titers in the subjects on these days begin to rise on day one after anti-serum in both cases and there's a very short period which is basically time zero where people don't have any anti-rabies antibodies in their circulation as opposed to the vaccine-only treated patients which, of course, takes a lot longer to develop antibodies against the vaccine. So, again it is this window that the rabies monoclonal antibodies need to cover and the window that apparently the licensed products do cover. This

is a little more about the international standard for anti-rabies serum developed in 1955, this is -- was an equine serum and it was defined to be 86.6 IUs per ampoule, and that was the original definition based on potency in one milligram of material. Now, finally in 1984, presumably this was running out, there was a first international standard for rabies immunoglobulin, so an HRIG was purchased by us as a standard preparation, it was filled by WHO, and there was a collaborative study that linked the potency of this preparation to this one, and again in 1994, we had the second international standard for rabies immunoglobulin which was linked to this, which was linked to that, so there's been a continuous line of standards, and that's nice to know when you're comparing studies. Cutter then performed, in order to license their product, clinical studies in healthy volunteers using their product called HyperRAB in support of licensure. The main study for this was conducted at University of California, Davis by Cabasso and colleagues and

it's a very simple study. There was HRIG, their product plus duck embryo vaccine, an HRIG-only group, and a duck embryo vaccine-only group, and the HRIG was given at 10, 20, or 40 IUs per kilo, i.m. of course, and the vaccine was given on a 14-dose regimen and was boosted on day 23 and day 33. The CDC did a smaller study looking at HRIG plus DEV using a different vaccine regimen, two different regimens. They were still 14-day regimens though, and HRIG only, but at the dose solely of 40 IUs per kilo. They used a CDC product for the lower doses and vaccine only. And this is the dose that was selected, which was 20 IUs per kilogram for patients receiving anti-rabies serum and you can see here this is in the context of receiving vaccine. This is one of many graphs in this paper. I'm showing it to you because it is a licensed dose and even by day one, you can see that the anti-serum has caused a rise in antibody titers in the subjects and then the vaccine kicks in. It's a pretty typical curve. The 20 IUs per mL was chosen because it seemed to

have the least interference with vaccine and still have a very robust early set of titers in the patients. So even though this was licensed in 1974, in 1972 the FDA was already reviewing the files. We didn't have user fee deadlines and there was more work to be done actually after the submission came in. And this is what the review extract says, and this is the FDA's rationale for licensure. Control clinical studies reported in support of this license application have demonstrated that when used as recommended at the rate of 20 units per kilo of body weight in man, and in conjunction with the Eli Lilly duck embryo rabies vaccine given as recommended, a rapid rise in neutralizing antibody results without interfering with later antibody inducement by the vaccine. No known prevention of rabies exists with the exception of circulating neutralizing antibody. Because there is no known treatment for rabies once symptoms developed, control clinical studies of efficacy cannot be done in man. Therefore, neutralizing antibody produced in

recipients of this product without interference with antibody production by vaccine is accepted as ample evidence of efficacy. Now, I think we should also, though, in addition to that, consider what else the FDA was considering. They were considering the clinical trial of heterologous RIG in the rabies outbreak in Iran and some case series with HRIG in the USSR, but the latter are a lot less detailed and not as convincingly analysed. All of these, though, were fairly small studies and there were varying serum and IG doses within those studies, nevertheless result still favored passive immune therapy, particularly for Category 3 exposures. Also, the pharmacokinetic data in humans suggest that early anti-rabies antibody titers favored survival. There were previous animal studies that also supported the efficacy of passive immune therapy, however equine RIG, or ERIG as we call it, was associated with serum sickness in anywhere between ten and 30 percent plus of patients who received it. So, this was considered to be a problem, because some

of these serum sickness syndromes are fairly serious. The FDA stated also in the federal register, but of course this is in 1980, that rigidly controlled field trials in men are not possible, but overall in considering the benefit risk of treatment with HRIG, it's obvious that it should have been licensed and it was. At that time, there were two products on the US market that were heterologous anti-serum. We have looked for those licensing files but so far have not found them because they were -- those products were discontinued in 1990 and the records may have been destroyed, unfortunately. But we're still looking, don't lose hope. There's one more product licensed in the US since then and this is Imogam HT which was licensed in 1984, and that licensure was based on literature supporting the concept of passive immune therapy and another pharmacokinetic study using Imogam 20 IUs per kilo plus rabies vaccine, which was their Imovax, versus rabies vaccine only and Imogam only, and you see in that study which was also published

that with the serum or the HRIG, there is an early rise in antibody titers. They looked at two doses, 44 IUs per kg and 20 IUs per kg and then the vaccine begins to work. So, just in thinking about all of this, there are some other observations that could be made. Clinical field studies are relatively limited and historical, but experience with the licensed HRIGs also suggested failures are extremely rare. HRIG products given at 20 IUs per kilo do not yield what are considered protective titers, which would be 0.5 IUs per mL for vaccines. But it's a very different context and some of the possible reasons for this are the -- well, one is that you don't need that much at the beginning or onset of a rabies infection, but also serum measurements might not reflect tissue levels achieved with a recommended infiltration of wounds with HRIG. Also, vaccine antibody responses may be a correlate of cellular immune responses. So, it's not really clear the extent of which non-humoral mechanisms might influence vaccine, but at the

very least, antibody is a marker and at the very most, it's probably quite important nevertheless. HRIG delays but does not prevent rabies in animal studies that suggest it slows but does not eliminate rabies entry into the nervous system. The animal models aren't quite like human models in that most animal models have short incubations, really very short compared to those in humans. Nevertheless, overall the onset of antibody action earlier and the duration of that antibody action are likely to be important considerations for monoclonal antibody effectiveness. Thank you for your attention.

DR. BIRNKRANT: Thank you very much. Our next speaker is Dr. Henry Wilde, who is a professor of medicine and infectious diseases at the Chulalongkorn University in Bangkok. Dr. Wilde is a member of several WHO expert committees dealing with rabies and vaccinology. Dr. Wilde is also a co-editor of Asian Biomedicine and has published over 300 papers in peer review journals and textbook chapters. We look forward to your

global perspective on the current standard of care for rabies post-exposure prophylaxis. Thank you, Dr. Wilde.

DR. WILDE: Well, thank you for inviting me. I'm a little bit frazzled right now, I've come from Geneva to Moscow then here and I'm a little bit jetlagged too. You are asking me to talk about a subject which is dear to my heart and has been for 20 years. We -- I work at Chulalongkorn University, which is a 1,500 bed hospital. So, we, you know, did a lot of work with rabies over the years, but I will not talk about standard treatment of rabies because Betsy Miranda, my friend of many years from the Philippines has just as much, if not more experience, and she will go into the details of what you face in the real world. Because what we're usually talking about is the western world, and that's not the same rabies, it's not the same problems, and it's not also what you -- not you, I speak by you the western rabies people that are going over this great new product that we're going

to be discussing, you know, the immune globulin. We're not going to face this. You're going to face, as I will try to explain to you, exactly the same problems that we faced with manufacturing the first ones commercially to readily available to manufacture ERIG, equine rabies immune globulin, which did not have a 30 percent reaction rate. These were the ancient figures of the first (Inaudible) purified products. It was a very good and still is a very good product. The reaction rates now with the pepsin digested ERIG are somewhere in the vicinity of one percent or less. So, it's a good, safe product. These are reaction rates for serum sickness, not minor ones, you know, itches and whatever. So, let me talk to you about what I think -- personally think will be the problems that you will face to introduce what you are going to, I hope, introduce. I reviewed the paper from the Indian Immunological, which I think has not been published yet, but it will be. There were two reviewers, I was one of them. We both said almost the same thing and recommended very

strongly to have it approved and manufactured. So, this is coming and in due course, it will eliminate probably certainly HRIG because HRIG is a no go, we don't even talk about it in the real world because it's not affordable, it's not available, period. So, ERIG is what we're using now, and ERIG will have to be continued to manufacture. So, let me kind of give you a little bit of an overview of some of the problems. Let's see how that works. All right, first of all, we really have numbers which are a joke. The numbers that we have are estimates, very crude estimates, they mostly come from people sitting in glass towers in Europe or the United States that have never worked in a field hospital looking after patients and don't have accurate numbers of case reports. They actually do not exist, period. And I can substantiate that for you with literature references which you can get yourself from Google or from (Inaudible). We don't know -- Francois Meslin, who was the last decades a director of rabies for WHO and a good friend of ours who was

out in the field all the time, he estimates that there are around 100,000 people dying of rabies and most of them are not being reported. The Philippines, the Ministry of Health, I think, with the help of one of our upcoming speakers, reported on 2,000 cases of rabies that were actually reported to the Ministry of Health and investigated as well as that could be done. Zero of these almost 2,000 people ever saw any medical or nursing officer. They had no post-exposure treatment. So, this is in the Philippines, which along with Thailand is probably one of the better countries in Asia. So, this is the real world and these are the people that you will have to -- not you, but whoever's going to make the stuff will have to sell the stuff and make it available. And the first thing that you're going to have to be facing is that it's going to be cost-effective because these people don't have any money, they don't have money to get the drug that's being charged or to travel for three -- at least three trips to a medical center somewhere nearby. And

you know, unless you can meet some of these needs and meet the same problems that we had with ERIG because the Thai Red Cross is one of the two major -- well, only really acceptable manufacturers of ERIG worldwide. Unless you can meet those, or better them, you're not even going to sell the stuff just like you're not selling HRIG. So, these are your real problems in just a few words. And I already mentioned this, let me just skip over so we have some time for answers. But, you know, it's obvious we can just see on there the faults are out there and they are not even being imagined by you. You know, there are doctor or regional nurse when she comes in, someone brings in a dog bite case, that she'll smear curry on there, which is a common treatment. Both in Philippines and Pakistan, curry is supposed to kill rabies virus. So, this is the kind of stuff you are going to be up against. Now, you can say we're not, we're the US FDA, we're primo people, and we're working for our own country and our neighbouring Canada, et cetera, et cetera, and

they, of course, can meet all these people. They're going to see a doctor, a real doctor who knows what rabies is, or a nurse who is maybe even better, okay. So, this is the problems. And the problems are these things. You know, when you see a wound like this, this is a wound, my nurse in the outpatient clinic that saw this patient was a smart nurse, a really smart nurse. She saw the ruptured tendon. You know, her job, they usually take care of this themselves, they don't call us. She put a clip, a mosquito onto both ends of the cut tendon before it can disappear. They disappear somewhere up and then you got a big problem. And she called me and I haven't done a tendon repair since my internship many years ago, very many, but I did it, I did it, you know, because I was challenged. And it was probably unethical that I did it because I could've transferred the patient over to the orthopaedic department at the university hospital, but the patient had a good job and did not get rabies because she also infiltrated the wound very

carefully with equine rabies immune globulin and killed the virus. We think, though we have no proof that the dog injected any virus because about 30, 40 percent of dogs that have rabies do not excrete the virus in the saliva. So, you see, that again tells you about numbers that we just looked at. You know, they're from the air. Almost, not all, but most of them are, they come from the field. So, we really don't know what we're dealing with, not that that should stop you from doing what you're doing, I'm delighted by it and even though I reviewed this paper and was not allowed to talk about what I read, and I'll tell you right now in public it was a first-lass paper and a first-class study which is going to appear and I think you're going to approve that product eventually. That's my opinion without being really involved in any way. So, there's hope and I went to the director of the Thai Red Cross, he was my year-long mentor and friend, Professor Visith Sitprija, and I told him, 'You know, you guys are going to be out of business with your

ERIG manufacture.' And he says, 'I'm delighted. We're losing mountains of money, the Red Cross is paying for it and nobody's buying it.' And you're going to meet that too because you're still going to have to inject the wounds. The one thing that people really hate when you tell them, 'I've got to take that hand or that leg or that face and I'm going to infiltrate this stuff into the wounds.' And I presented -- I've been preaching wound injection for 30 years, I think, around Asia, maybe more, at meetings, and I have many years ago a very respected Indian gray haired professor, more gray hair than I am now and say, 'What you're saying is nonsense. It's against all medical principles. You inject a dirty infected wound with a foreign substance.' This is the kind of stuff you're going to be up against, be prepared. And it's in some ways legit, though we actually, because of this character, you know, challenging me at a big meeting in New Delhi or whatever it was, you know, agitated me, so we did a study, a large study in two major medical centers in

Bangkok by very competent academic people where one group had dirty wounds injected with local anaesthetic because of suturing and the other group had them injected only with ERIG and the infection rate, I think, was something like 12 percent. It was about the same, makes no difference. You wash the wounds, treat them with antibiotics appropriately, afterwards it make no difference. This is what you're going to meet again, it's going to come to you once you introduce this product, which you will, and I hope you will. So, this is, sort of, where we are still. Have fun. We had fun and we spent some nights not sleeping well because we did things to patients without the backup of WHO or the US CDC or whatever. You know, we did them because of logic because a lot of stuff in rabies, you cannot do a controlled study. No one will let you, no ethics committee will approve you. Actually, your serum that is coming, and there are three products my spies tell me that are in the pipeline, it's not only the one we're all hoping for. These

products will meet the same problem, you're going to have to go through local, not just internationally, WHO, but you'll have to go through local approval agencies and some of those people believe they are stupid. They will object to things that they know -- they should know logically make no sense, there's no way you can do that. You know, you can't tell some people that are bitten by a proven rabid dog you're going to give them whatever proper treatment and the other you're going to do an experimental one. Try and get ethics committee approval in India or anywhere, forget it. And you get it, you have to go on your knees and see each one of those people individually and talk to them. This is what you will face. Well, the other thing is, you know, you come up, my colleagues and friends at WHO and at the university, they will say, 'Well, you know, how can you categorize patients?' That first slide I showed you, that's from a rabid dog and I would have put the prognosis on terrible on top of a cut tendon which I, you know, an amateur was

suturing, putting together, trying to remember how you put those sutures, you know, the ways I was taught, you know, and the patient survived. Here is one, you can see, this slide was done on the same day that the dog bit this person and you can see the infection already -- actually it was a cat, cat bites really get infected fast. They have a blood -- you know, Pasteurella multocida which just goes wild when it gets into tissue. And this was also a rabid dog. And the risk here may be higher than the first one, I don't know, nobody knows. So, it's very difficult to even categorize, so there, how are you going to do an US FDA approved study, you know, when you don't even know, you know, if this was really an infection because on top of everything else, the saliva may not contain, even a crazy dog. We've actually -- you know, we have a lab at Thai Red Cross which belongs -- doesn't belong, but it actually belongs staff-wise to the university, is staffed mostly by people part-time, you know, from the medical school. And you know, they have all

the facilities. Within three hours we can get an FAT done if we have the dog. But you can't do that on all and you can't do it if you are out in the countryside, and that's where the rabies is. It's not here in your city or in my hometown, Juneau, Alaska, but it sure as hell in a village up in the mountains where there is nobody, there is no post-exposure treatment and it's neither diagnosed nor treated. So, you don't know, you can't tell, it's on the hand, that's a very bad thing, okay. And what about this one. This one was a kid that -- actually our nurses in the outpatient clinic called me over when I was doing something else at the hospital and, you know, when they called me, I always worry, because we're using ERIG, that they have anaphylaxis. So, I jog over there, across the street, don't to get run over by a motorcycle and gasping for air, and they show me this kid and they say, 'What do we do with this kid?' Well, I said, 'It's a Category 3 exposure. You know, call the intern,' or whatever. In this case, I probably would have

called a surgeon, you know, to do a nice repair. And, 'You know, why are you calling me?' Well, they said, 'We calculated the ERIG dose on the base of weight and the dose was two point something CCs. How are we going to inject all these wounds?' And, you know, I never thought of that either because I never actually saw a patient like this. You don't see them very often, but you do in a busy -- in a mobile clinic. So, I did what I would and you probably would do. I looked at them, they all stood around, there are about ten of them on staff and I said, 'What do you think,' to gain time. And nobody said anything and then one of the girls that I considered one of the least smart and experienced, she said, 'We dilute the ERIG, don't we? Doesn't that make sense?' Well, about six months later we had two or three cases like this, they all survived, we diluted it, and I presented this at the WHO expert committee and they said, 'What proof do you have?' I said, 'I've got three cases.' And I don't know whether that dog has rabies in the saliva, so I

couldn't really prove anything, it was just observational. And they hemmed and hawed and these are all, you know, European professors from glass towers. Not all, Betsy was there, weren't you? And, you know, they said, 'Well, it makes sense,' and it's in the guidelines now. So, this is a good example of something that by now everybody knows, it's logical, you know, because we don't know how much, you know, there was actually -- well, we do, we calculate it, you know, how many antibodies there are, but that varies when you say dilute. Dilute means you dilute as much as you have to to inject all the wounds, because if you inject too much, if you, you know, just double, triple, quadruple, the dose and inject it all with pure ERIG, HRIG, or whatever your product, you know, it may suppress the antibody response because the natural response to having an exogenous antibody injected loses the incentive for the real stuff. So, these are examples of what is going to happen when you study a product. Well, I think Dr. Taylor already

talked about some of this and I already mentioned the study from the Philippines of the 2,000 -- almost 2,000 cases of deaths, none of which had any treatment. And most of these people had no treatment because it wasn't available and they're on islands or on mountaintops somewhere with no education and no one to give the vaccine. And vaccine alone -- remember that too, vaccine alone will save lives because this business with a window period only works because there's got to be a nerve nearby that the virus can crawl and attach itself to (Inaudible) receptors and then start going up the nerve to the brain and it's in a protected environment there. If you develop antibodies later on with vaccine, they don't get there, you see. This has been well-established and I think I -- in the box, you know, the box that we have, the WHO component of this meeting, there are all kinds of papers substantiating all these crazy statements that are all mostly purely from experience, not from scientific studies. We do scientific studies too, but in this field, you

cannot. Well, you know about the window period, you know, obvious, there is at least seven days of, maybe more and maybe ten days where, you know, the virus is left alone, there is no antibody unless you inject it, but again, most virus is inoculated into tissue which doesn't have a nerve handy there to crawl in. So, most people will survive. And that's why we inject the wounds, it's pretty obvious. Here is another study that was just done by Chinese people, Dr. Wu (ph), I think -- wherever, in a good center, well-known center, he did a mouse study with horrendous doses of vaccine and he showed here that even in mice, it's over ten days or almost ten days before the window period is over. Just published now, brand new. We've known this for a long time. And so to show, you know, how long the virus stays in the wound we did -- we went to the university hospital isotope lab with some hamsters, I think it was, you know, some immune globulin, and while they were busy or looking away or we bribe them, we did a isotope study with immune globulin to show, you

know, that the stuff hangs around right there in the wound for at least two days. So, you know, even if you don't get it right way, you know, you got a prolonged study, but not much longer. If it's much longer than three days, we -- that's a guess, we have no proof for that. It probably does more harm than good. Well, that's why we inject, and it's painful thing, nobody likes to do that. I run away, you know, from a patient like that and let the nurses do it. I can't face it, it kind of hurts me. And when you get into this kind of a business, you know, the eye is a horrible place, because that's just like a nerve, so what do you do? And we've actually called an ophthalmologist with a eye injury, a corneal injury and he injected, I forgot what it was, HRIG, I think we bought some HRIG at a private pharmacy into the globus and we got away with it and it was a rabid dog. So, you see, we did that without ethics approval, we did that without even some kind of research approval, because these things come up. We did another one too where we

had a rabies patient after the -- not disaster, but the marvellous recovery of that girl in Milwaukee, you know, who developed her own antibodies, her antibodies in the spinal fluid as well as in the serum on admission. We did -- we had a woman coming in, 37 years old, nice woman, fully conscious, intact with furious rabies, you know, the -- she had all the symptoms, you know, retraction of the muscles in the neck and so on, aerophobia, hydrophobia, there's no question that she had rabies and we've proven that. And I had some HRIG that we had manufactured, we do manufacture a little bit of it, it's very difficult, expensive, and the donors are hard to find. So, anyhow, I had some that was about to be outdated in a month or two or three in the refrigerator. I had something like 300 ccs. And my colleague from the emergency room came and said we got this patient, he knew about the ERIG -- the HRIG that we were looking to give to somebody IV. So, we gave it IV and now we have to get some more because she got better, we converted her from

encephalitic rabies to systemic rabies. She developed cardiac arrhythmia and with IV HRIG to be outdated, the cardiac arrhythmia stopped, she went back to sinus arrhythmia. She tied us up for about seven days. I mean, there were three senior staff people who had nothing else to do, plus one half of the emergency room were totally preoccupied with this patient who lived for about 14 days, the case is published, you can look it up in internet. So, this is the sort of thing, you know, that we have to do and people in India and other places do. So, your stuff is going to come extremely welcome, and I know the Thai Red Cross will thank you for getting them off. They will still have to make their snake antivenom, we got a big horse farm, you know, because that -- you're dealing -- that's not easy like this, you're dealing with enzymes, you're dealing with proteolytic stuff, you know, about five or six epitopes that you have to get rid of. I think I'm going over my time and I'll quit because there will be time to discuss some other stuff. Yes, I

said that already. Okay? Can I leave?

DR. BIRNKRANT: Yes, thank you very much. Well, the next group of lectures relate to various perspectives on rabies monoclonal antibody development. We'll have Erin Sparrow from the WHO, we'll have industry and academia representations. Let's begin with Erin Sparrow who has been with the WHO in Geneva for ten years working in both the immunization and medicine departments. Prior to joining WHO, she worked for The Global Fund. One of her roles at WHO has been to monitor the development of affordable monoclonal antibodies to replace RIG and rabies post-exposure prophylaxis. Thank you, Erin.

DR. SPARROW: Thank you. So, I want to start by saying thank you to the FDA for organizing this really important workshop and bringing together so many different stakeholders. And thank you to Henry because that was a fantastic presentation that really described what the issues are in developing countries with regards to rabies post-exposure prophylaxis. So,

just for a very quick presentation on the WHO perspective with regards to monoclonal antibody development to replace or complement blood derived rabies immune globulin is that, of course, the main reason for developing monoclonal antibody product is to address some of the limitations of the blood derived RIG and the limitations are really the availability. There is a global shortage, especially for HRIG in developing countries, and for the equine products more and more manufactures have been dropping off the market in the last decade or so. There's also issues with affordability, HRIG in particular is very expensive. And for both HRIG and ERIG, it's often paid out of pocket by the patients themselves and they are given a choice about whether or not they want the vaccine which is paid for by the public sector, or they want to pay for the HRIG or the ERIG as well. There's also some safety concerns although purification techniques over the years have greatly improved and so anaphylactic shock, as Henry described, are now

seen in less than one percent of patients. But it is interesting that, you know, you see that image there on the right that, you know, we're still using horses as our bioreactors today, yet we've had decades of recombinant antibody technologies available. So, monoclonal antibodies could address some of the limitations, they could complement the supply, leading to more supply on the global scale. They also could have reduced production costs although monoclonal antibodies are actually quite expensive to produce, the amount of antibody needed in post-exposure prophylaxis is very small, so the cost is actually not too expensive. Also, it could reduce the risk of adverse reactions, especially with regards to ERIG, and you'll also have an advantage with neutralizing monoclonal antibodies, so you've got to concentrate the amount of neutralizing monoclonal antibodies in your monoclonal antibody product or cocktail compared to polyclonal serum derived RIG which, you know, some people might argue that polyclonal you have more, but actually

often those antibodies are non-neutralizing. So, there is that advantage of monoclonal antibody products. So, rabies monoclonal antibody development has actually been on the WHO radar since 1990, this was well before my time at WHO and it was first discussed in 1990 at the Sixth Consultation on Monoclonal Antibodies and Rabies Diagnosis And Research. And at this particular consultation, they mapped out recommendations and next steps for further development of these products. And it wasn't until 2002, so 12 years later, that there was actually a plan that was actually put forward and this was at a WHO consultation on rabies monoclonal antibody cocktail development. And they brought around the table all of the WHO collaborating centers and these collaborating centers agreed to donate monoclonal antibodies that have been collecting throughout the years through WHO, who would then donate these products for further development to manufacturers. So, the overall goal of this project was to make monoclonal antibody products

available to replace or to complement rabies immune globulin and that the end goal would be to make these products at the lowest possible price available for developing countries. So, the first phase of the project which began in 2002 to 2006 was really to select and evaluate potential monoclonal antibodies which had been donated by the WHO collaborating centers. A short list of these monoclonal antibodies was selected, they were brought -- brought the neutralizing, they also had different epitopes. These were then transferred to three manufacturers, Zydus Cadila in India, who is going to be presenting later on today, CSIR in South Africa and Span Biotherapeutics in India. And of those three manufacturers, only Zydus Cadila has been successful in actually taking that product development forward and that's been primarily due to funding constraints for the other two manufacturers who just weren't able to raise the funds to take their products from the pre-clinical into the clinical trial phase. WHO has also been

monitoring the field just to see what other products are being developed independent of the WHO project and this table just shows a list of those candidates that have reached clinical trials. So, Crucell, which was a -- which is a Dutch biotech company, developed a monoclonal antibody cocktail and they took it all the way through to phase two clinical trials and you can see the number of trials that they actually conducted. Unfortunately, they were bought up by Johnson & Johnson and they decided to stop product development after phase two because they didn't have the necessary financing or they didn't want to commit the necessary financing to do a full scale phase three efficacy study. There's also RMAb which has been a partnership between MassBiologics and also the Serum Institute of India, and you'll hear from the Serum Institute of India after my presentation as well. And they did a phase one in India followed by a phase two/three and their product was actually licensed by the Indian authority last August. The product has yet

to be launched, but this could be a game-changing product. This -- as I mentioned before, the Zydus Cadila product which uses the monoclonal antibodies donated by WHO and they will be initiating phase three sometime this year. There is also a couple of other products that have reached clinical trials, a product by Synermore, which is a Taiwanese company, and they are currently recruiting in a phase two clinical study and there is a also a Chinese-US partnership between MTTI and a north China pharmaceutical corporation and they have been conducting a phase two for a while, but we actually are not sure how that product development is going because we haven't received any updates for a number of -- for a couple of years. So, we've been talking about this since 1990, so 27 years later, we still don't have a product besides the Indian one that's only just been approved last year and that's because there are lot of challenges to bring these products forward. And I would say that one of the biggest challenges has been funding. Costly

preclinical development, costly clinical studies, and the return on investment for pharmaceutical companies is not so clear. This is rabies, it's a disease that primarily affects developing countries, would the product be used, would you make it through to licensure, all of these questions make it difficult for pharmaceutical companies to justify investing these huge amounts. And I think that's one of the main reasons why the Crucell and Johnson & Johnson product has not been taken forward. There's also questions about how to do a phase three efficacy study and that was touched upon by Dorothy, so I won't go into any details there. But these are questions that pharmaceutical companies are faced with when they're trying to bring their products through the clinical trial phase. And there's also a question about registering the product in other countries, so India has the first product, but how are they going to get that product licensed in other countries so that they can be used in the populations that need the most. So, even once we

have these products available, there's also a lot of challenges for uptake and use and this is exactly what Henry was talking about. You've got to try and convince the doctors, the nurses, there needs to be a decision by policymakers to include monoclonal antibodies in post-exposure prophylaxis. There needs to be a WHO recommendation made and this would be made through the SAGE, the Strategic Advisory Group of Experts on immunization. It will also need to be included in the WHO essential medicine list. We need to determine the cost effectiveness of these products. We still don't know what the price will be. This will depend on economy scale. This will depend on many factors. We'll need to revise the treatment guidelines to include monoclonal antibodies in the post-exposure prophylaxis recommendations. Maybe there'll be need for training of healthcare workers, storage conditions may or may not differ from standard RIG. And then of course, there's the whole procurement and supply issues, and this could be facilitated by UN

procurement or bulk purchase. There's also the possibility for WHO pre-qualification which is often a prerequisite for purchase by UN agencies. And then there could also be possibilities for stockpiling these products. I mentioned in the last slide that SAGE would have to make a recommendation about the inclusion of monoclonal antibodies in the WHO post-exposure prophylaxis recommendation and actually the SAGE working group on rabies has currently been reviewing monoclonal antibodies for RIG and they will be presenting their recommendation to the next SAGE meeting in October this year. So, we have to wait and see what the recommendation is, but I think it's going to be quite positive, so just -- yes, keep your eye on that website there and see it should be announced shortly after that SAGE meeting. So, thank you.

DR. BIRNKRANT: Thank you very much, that was quite helpful. Our next two speakers are from industry. Our first of those is Samir Desai, who heads the Biologics and Vaccines business unit of

Cadila Healthcare. He's been associated with the pharmaceutical industry for 30 years and has worked with vaccines and public health for 20 years.

MR. DESAI: Thank you for the opportunity to share the experience of developing RabiMabs, monoclonal antibody cocktail for post-bite prophylaxis against rabies. This is a collaborative product with the World Health Organization (Inaudible) taken up by Cadila Healthcare Limited. The slides -- the introductory slides, as has always been pointed out, there has been a need to develop anti-rabies monoclonal antibodies and as we all know, the neutralizing antibodies are targeted against the G protein of the rabies virus. The 2002 consultation that was referred to also came up with the recommendation that developing a single monoclonal antibody candidate concentrating the breadth of rabies virus and the geographic dispersion may not really be an appropriate strategy and it may be better that two antibodies

are combined to create a cocktail of monoclonal antibodies. So, getting straight to the product RabiMabs is a normal cocktail of two murine monoclonal antibodies which are donated by WHO partnering centers, CDC Atlanta and ADRI in Canada, M777-16-3, which is an IgG1 monoclonal antibody which binds site II on G protein of rabies virus envelope and 62-71-3 which is IgG2b antibody binding to the site III. It's important to note here that these are non-overlapping sites and that in a sense helps with the risk mitigation as the binding of the RabiMabs product to two distinct antigenic sites provides increased protection against a mutated virus -- rabies virus that might have lost an epitope due to a mutation. To address the issue of breadth of rabies virus neutralization, let me inform you that extensive in vitro and in vivo neutralization studies were conducted with these antibodies at different WHO collaborating laboratories like FLI in Germany, CDC Atlanta, Wusterheusen in Canada, and National Institute of Mental Health and Neurological

Sciences in Bangalore, India. These monoclonal antibodies have been tested for neutralization of viruses isolated from a variety of domestic and wild animals from a variety of countries to count for the geographic diversity in terms of the rabies virus dispersion, such as dogs from India, Turkey, Ethiopia, Mexico, Nepal, et cetera. Foxes from Europe -- from eastern Europe, polar fox, wolf from Sarajevo, bats from Europe, and a variety of animals from the United States. This, to some extent, addresses the issue of the breadth of rabies virus neutralization studies and I take you through the studies, the in vivo potency studies that have been conducted so far. Notice the graphic here -- the tables here present the conducting center, the center that has conducted the experiment, the animal models employed, the challenge virus strain and the radius groups, the dose as well as the route of administration, the survival data, and what is evident is that an equipotent mixture of these two antibodies was found to be highly efficacious in hamsters

challenged with lethal dose of rabies virus in these two studies listed here. Similarly another study conducted by the CDC again, but with different challenge virus strain, again in a hamster model, produce high efficacy, showed high in vivo potency of neutralization and survival data. This is the study conducted at the National Institute of Mental Health and Neurosciences, India. Mice model challenge with ten different strains, eleven different street isolates of rabies virus, mainly dogs -- from dogs and you can you see this was compared against RabiMabs, two different dosages were compared against HRIG and ERIG in equal doses and you could see the control group as well and as you would find that RabiMabs was found to be equally potent with both human RIG and equine RIG in mice challenged with lethal dose of 11 different street isolates of rabies virus from dogs in India. These are two studies conducted at the Zydus research center at Cadila Healthcare Limited, again hamster models, CVS-11 challenge virus, you have the standard HRIG and

the test product that is RabiMabs and as you would see, RabiMabs, which is an equipotent mix of two monoclonal antibodies, was found to be highly efficacious in hamster challenged with lethal dose of rabies virus. So, the virus neutralization activity of RabiMabs, the product is formulated to contain an equipotent mix of each antibody which is determined using a pharmacopeial assay using a RFFIT assay using the CVS-11 virus strain. It's a highly purified product with much lesser protein per dose. The advantage of neutralized -- concentrated neutralizing antibodies as was alluded to in the previous presentation, it can be produced in scalable quantities like any other monoclonal antibody. The organization that I represent has extensive experience in commercializing monoclonal antibodies and has extensive manufacturing capabilities for the same. So, this here is the details of the formulated product. It is formulated as containing 3,000 international units of the product, an equipotent mixture of both antibodies, meaning 1,500

international units each in a 10 mL formulation, much like the equine rabies immunoglobulin formulation for easy adoption and the extractable volume during administration is 10 while fill volume is 10.5. The product has completed -- the clinical trial batch has completed 36 months of stability studies and it is a stable product at standard conditions between two degrees and eight degrees Celsius. The product has also completed 12 months in an accelerated storage condition at 25 degrees. Essentially, one can conclude from this that the product is stable in the formulation that has been developed. Let me straight now come to the clinical status and the clinical development part. Phase one study of the product was completed with three different dosages, ten, 20, and 40 international units per kg dose of RabiMabs. The 40 and 20 clearly came from the HRIG and ERIG doses as recommended and the ten was an experimental dose. Phase two study has been completed with 40 international units per kg dose of RabiMabs with rabies vaccine VaxiRab N

following the recommended post-exposure prophylaxis of five dose regime. And the phase three protocol which has been approved by the Drugs Controller General of India which begins soon, hopefully next quarter is a randomized, multi-centric, open-label, comparator-controlled study to evaluate the efficacy, and most importantly safety of RabiMabs administered in conjunction with VaxiRab N for post-exposure prophylaxis in patients following potential rabies exposure. The total number of patients who had been exposed to the product in phase one and phase two studies are 41 total subjects. The clinical assay being used is the pharmacopeial RFFIT assay, which is to WHO international standard. It is an assay useful in determination of antibodies against the rabies virus in both early as well as late phase which represent the passive and the active immunization phases of the drug product and of the -- induced by the vaccine, assay is pharmacopeial and is currently used by the industry and used in laboratories worldwide. To

give you more details about phase one study that was conducted, the objective was to evaluate the safety, tolerability, and neutralizing activity of RabiMabs against rabies virus in healthy subjects. There were three panels of eight healthy volunteers each, six in each received the drug product in three different dosages, ten international units per kg bodyweight, 20, and 40 international units per kg bodyweight respectively and six healthy volunteers received a placebo. The mode of administration was single dose in lateral thigh muscle and 40 international units per kg bodyweight, equal volumes of two injections were administered into the left and right lateral thigh muscles. The graph here represents the geometric mean titers with the RabiMabs product with -- and as you can see, the titers increased in a dose dependent manner with 40 international units per kg bodyweight dose proving to be most potent and well tolerated, as you would see in the slides as I'm discussing the slides coming up next. Also important to see the kind of interest

-- see the kind of titers that are being achieved which are quite significantly higher than some doses reported historically with the rabies immunoglobulin products. There were no adverse events -- no serious adverse events in subjects. Interestingly, the anti-drug antibodies are not developed for the first seven days, which is the most crucial period for which the passive immunization must provide, the window period that has been talked about in every presentation preceding this one. We did see two subjects developing anti-drug antibodies between day 14 and day 42 but then, by then, the vaccine product has already (Inaudible), so this may not be clinically significant. Following this, the phase two study was conducted in -- again in 18 subjects, 12 healthy volunteers received RabiMabs at a dose of 40 international units per kg bodyweight. As you would recollect in the previous slide, that was found to be the most potent dose and well tolerated. So, on day zero, 12 healthy volunteers received RabiMabs in the dose of 40 international

units per kg bodyweight, plus five doses of vaccines, obviously administered in different sides, and six healthy volunteers received placebo in day zero, plus five doses of vaccine on zero, three, seven, 14, and 28 days. This is -- I'll skip this. This is a very interesting slide because as you would notice, by day three the product has already achieved significant titers these are about 0.4 IU per mL with 40 international units per kg bodyweight and as you would know, this is about 3x higher than the historically reported levels of either RIG products, the human or equine RIG products, as you would see in the slides that I discuss coming up next. It is also important to see that while there was a minimal utilization of the vaccine response, it was not clinically significant, with titers being achieved much higher than the protective levels as defined for vaccine response. And this kind of gave us confidence that the product provides significantly better protection, at least about 3x, if the titers can be translated

as providing protection, against currently available rabies immunoglobulin products, especially in the period when it is most needed, which is in the first three to seven days. This is just for reference rabies virus neutralizing antibody data with IMOGAM Rabies, which is an approved product. The levels the titers achieved, as you can see, are about 0.1 IU per mL and also with both the forms of equine rabies immunoglobulin, the titers achieved are somewhere closer to the same level of 0.1 IU/ml and as you would recollect, in the previous slide I showed that with RabiMabs, the titers achieved were about 3x or so better. Coming to the summary of adverse events in the phase two study, there were two subjects who had reported adverse events, primarily fever, burning micturition, and skin lesions and pain. Importantly, again, anti-drug antibodies were not developed in the first seven days. We do see anti-body antibodies between day 14 to day 42, but -- and almost all subjects, six out of seven subjects showed a reduced to nil ADA

response by day 42, by which time, in any case, the antibody is probably out of circulation. The details of the phase three study which is about to commence as I mentioned the randomized, multi-centric, open-label, comparator-controlled study to evaluate the efficacy, and more importantly the safety, because the antibody, the titers, et cetera, have already been demonstrated in phase one, phase two of RabiMabs administered in conjunction with VaxiRab N, which is a rabies vaccine manufactured by Cadila Healthcare Limited for post-exposure prophylaxis in patient following potential rabies exposure. The primary objective is to determine the proportion of subjects without RFFIT titer more than or equal to 0.5 IU per mL on days 14 who have received RabiMabs plus VaxiRab N and/or immunoglobulins, which is IMOGAM Rabies plus VaxiRab N. The secondary objectives are to check the proportion of subject with RFFIT titers more than are equal to 0.5 on days 28, 42, and 84, proportions of subjects with RFFIT titer more than or equal to 0.1 IU per mL as that is what is the

reference for product available currently and (Inaudible) RabiMabs vis-a-vis IMOGAM Rabies, incidence of local and systemic reactions up to day seven for RabiMabs and Imogam. Incidence of adverse events and serious adverse events during the study participation, and proportion of subjects with immunogenicity of RabiMabs on days 14, 42, and 84. For treatment arm a, RabiMabs 40 international units per kg bodyweight and VaxiRab N 1 mL on day zero, three, seven, 14, and 28. Treatment arm B would receive IMOGAM Rabies at 20 international units per kg bodyweight, that's a recommended dose, with the vaccine, five dose. A total of 308 subjects are to be enrolled, including a 20 percent dropout, concentrating some of the challenges that Dr. Wilde alluded to, there are patients who find it difficult to make it back for repeat vaccine dosing to the center, will be enrolled in a ratio of ratio of one to one to have a minimum of 124 subjects in each group, that is RabiMabs 40 international units or -- and VaxiRab or IMOGAM Rabies with VaxiRab. And the study is

likely to commence at the beginning of next quarter or the end of this one and we hope to publish the data once the study has been completed. So, in conclusion, the test product, RabiMabs of M/s. Cadila Healthcare Limited has been found to be safe and well tolerated when administered as single IM dose up to 40 international units per kg in healthy subjects. The pharmacokinetic evaluations indicated that the active drug is well absorbed in intramuscular administration in healthy subjects in a dose related manner. RVNA in phase two suggests timely administration of RabiMabs dose will provide better early protection after animal bite compared to available rabies immunoglobulin product. VaxiRab and was not significantly neutralized by RabiMabs at a dose of 40 international units per kg as the vaccine was still able to give titers well above the WHO recommendations of protective titers of 0.5 international units per mL after vaccination and for better assessment of efficacy and safety, a phase three study will be conducted

in category three animal bite subjects. Thank you.

DR. BIRNKRANT: Thank you very much. Our second industry perspective will be presented by Dr. Bhagwat Gunale of the Serum Institute of India. Dr. Gunale trained in clinical pharmacology at Christian Medical College in Vellore and has more than nine years of industry experience in clinical development in pharmacovigilance. Thank you very much for coming.

DR. GUNALE: I would like to thank FDA and WHO for inviting me for this talk and I will be presenting the experience in the development of rabies monoclonal at Serum Institute of India, both pre-clinical and clinical. So, this product is basically a technology transfer from MassBiologics which is MassBiologics, University of Massachusetts Medical School. In 2003, the research goal of MassBiologics was to identify human mAb which would neutralize the broad panel of rabies viruses which would be safe and

affordable alternative to RIG in places where the disease burden is high. So, the research began with identifying the mAbs, various clones were prepared of a suitable mAb which could neutralize a broad variety of natural isolates of rabies virus and that clone which produces the mAb should be of high potency and demonstrate the efficacy in the in vivo animal models as well as in vitro efficacy. So, HuMAb-Mouse was immunized which was from Medarex and immunized with a rabies vaccine followed by hybridoma production and several clones were isolated, so of which, one was selected which was RMAB1 which is also in the literature appears as HuMab17C7, RAB1, or MBL RAB1 now pronounced as SII RMAb and commercially named as Rabishield. So, in 2006, MassBiologics and Serum Institute signed an agreement to further develop this RAB1 or RMAB1 and during this time, already the RMAb was tested against a broad panel of isolates and at that time, the Crucell monoclonal was also under development. So, SII RMAb showed the neutralizing activity against 25

isolates of rabies virus, most of these were from US and the CVS-11, which is the laboratory adopted strain, and then the Thai strains and Argentinean and some Latin America and Mexican strains of rabies viruses, whereas the other cocktail mAb from Crucell did not show neutralizing activity against a few strains. Further, several isolates of rabies viruses from Asia were tested, from Nepal, India, Sri Lanka, and some of the isolates from Canada were tested and all these isolates were shown to be neutralized and the data was presented at RITA 2008. The hamster model which was used to demonstrate the protection against the lethal rabies, so these in vivo post-exposure prophylaxis experiments were conducted at CDC Atlanta where hamsters were challenged with access Texas coyote rabies virus and then the next HRIG or mAb was given at the site of inoculation and similar to the post-exposure prophylaxis regimen, that is the vaccine was given on day zero, three, seven, 14, and 28 and the survival end point was assessed on day 42. So, you can see with HRIG at

37 IU whereas RMAb was 20 IU, then five IU, and 0.2 IU. And you can see that at various doses, even at the 0.2 IU, excellent survival is seen with the RMAb, which is comparable to HRIG. SII RMAb alone also demonstrated the protection from the rabies in hamsters, with the various doses here were 26 IU, seven IU, and one IU and you can see at the lowest dose, that is 0.05 IU, survival was very less. So, even as alone, it -- the mAb alone demonstrated protection in hamsters. So, this -- the preclinical discovery was published in Vaccine and it was concluded that the HuMAb was the most promising antibody identified because it neutralized all rabies virus isolates tested and it recognizes a conformational epitope on the G protein at site III, which is the most conserved epitope in the rabies virus G. So, the HuMAb 17C7 showed protection in that in vivo model of hamsters against a lethal challenge of rabies virus. And a further clinical study that (Inaudible) would be generated by using the single mAb and (Inaudible) GenBank analysis was done and

RMAb showed the capacity for neutralizing all identified rabies isolates. Except that where a virus will have a mutation at two positions, that is 336 and 342 that would escape the neutralization. So, so far only the Peruvian bat isolate has been found to have such mutation which would escape the neutralization by RMAb. So, as RMAb neutralizes all currently identified rabies isolates, it protects the hamsters from challenge with rabies virus. It will be viable replacement for HRIG in PEP and strong -- the strong pre-clinical data paved the way for phase I clinical study. This is the chronology of the development, so the collaboration and licensing agreement with MassBiologics in 2006, tech transfer to Serum Institute 2007, and the bioreactors were inoculated to produce RMAb in 2007, and the first clinical lot was prepared in 2008, and between 2007 to '08 the preclinical talk studies were also conducted. Phase I study began in India in 2009 and completed in 2010. The phase II, III study begin -- started in India in 2012 -- June, 2012,

and the recruitment was completed, including the follow-up, in March, 2015, and the marketing authorization received in 2016. Coming to the phase I study, the design and conduct, it was an open-label, dose escalation study and in healthy adult volunteers aged 18 to 45 years. It was a simulated post-exposure prophylaxis regimen where MAb plus vaccine or HRIG plus vaccine was given. And initially the lowest dose was used considering the tragedy in UK which happened with the monoclonal, all the volunteers were admitted to the ICU. So, considering this, very cautious approach was used and the lowest dose of MAb was initially tested in two adults each. And after demonstrating the safety and approval from the DSMB, the subsequent enrolment in simulated PEP regimen was initiated. The end points were the safety assessment of adverse events and laboratory evaluations (Inaudible) chemical parameters and anti-drug antibodies. And the pharmacokinetics parameters were to measure the neutralizing antibody activity of HRIG plus vaccine group to

MAb plus vaccine group and determine the dose of monoclonal which is comparable to the HRIG and the pK parameters are assessed with only MAb only cohort. And the trial is registered in the Clinical Trial Registry of India as per the regulatory requirements in India. Safety results, two unrelated SAEs occurred during the one year follow up, of which one was simple, the patient -- the volunteer had not given history of injection reactions before administering the drug, but when the drug was administered and patient collapsed, but since the administration was done in the phase I unit, all the facilities were available and well care -- good care was taken and the patient was resuscitated. And the second SAE was suspected suicide and that was quite long after the -- during the one year follow up, that is post 80 to 84 day study period. There were 203 non-serious adverse events, most of them were solicited injection site reactions, either at the site of antibody injection or the vaccination during the 28 days. And 157 assessed as mild and most of

them did not require any aid to resolve on their own within a few days and the frequency was similar between the MAb group and the HRIG plus vaccine group and none of the participants had anti-drug antibody and the data has been published in Vaccine. So, coming to the immune antibody response or antibody responses with the various assays RFFIT, ELISA, and RFFIT with Flury LEP. Commonly the RFFIT is conducted using CVS-11 strain and in addition, we had done the RFFIT using the Flury LEP, which is the wild type of rabies virus, and at day zero baseline, the titers of antibodies were comparable and you can see on day three the titers are slightly elevated and they -- they're progressively increasing with each dose of vaccine from day seven onwards. And the titers were comparable with RFFIT using CVS-11 at all time points except for day 42 where the titers were less in SII group, but this is not clinically relevant. But when it is processed with RFFIT using the Flury LEP, you can see that there is a significant elevation of the titers on day three

that is 7.54 n the RMAb group as compared to HRIG group, it is less than 0.5 which is WHO (Inaudible). So, this data and the titers were significantly higher by using Flury LEP strain at day seven and day 14 time points. In addition, the ELISA assay was done to assess the antibody titers and again at early time points, that is day three and seven, the titers were significantly higher in the MAb group. The GMTs by CVS-!! RFFIT were comparable between the groups except for day 42. GMCs by ELISA and RFFIT Flury LEP was significantly greater on day three and seven which indicates that it provides early coverage when the vaccine is not going to provide the protection and so the study's already published in the Vaccine. So, based on these data, phase II and III study was planned in patients with potential rabies exposure. And again, the cautious approach was used, so the study was divided into part one and part two. So, part one had 50 subjects who had category three exposure to lower extremity only, considering the low risk of exposure and each

group had 25 subjects with potential rabies exposure and the regimen was standard (Inaudible) regimen day zero, three, seven, 14, 28. And the blood samples were collected at all these time points, (Inaudible) response by RFFIT and ELISA, as well as the safety was done by estimating the anti-drug antibody concentrations. And interim analysis for futility was conducted after day 14 samples of these 50 subjects were analysed and it showed that the futility is not met and the DSMB reviewed the data and recommended the continuation of the study into part two. In part two, 150 participants with WHO category three on any part of the body were enrolled and the similar design was implemented. The primary end point was the ratio of day 14 geometric mean titers of antibodies measured by RFFIT of SII RMAb plus vaccine group compared to HRIG plus vaccine group given as a post-exposure prophylaxis. Enrolment was started in June, 2012. Again the regulator had issued permission to enrol only adults and post-menopausal females with exposure only on

lower extremity presenting within 72 hours of bite and the condition for enrolment of children was that we submit the date of first ten adults about the safety and then the data for the safety in first ten adults was submitted on 31st December, 2012. And the subject enrolment for part one was completed in -- on 14 Jan, 2013. The interim analysis for futility of the first 50 participants with day 14 RFFIT was performed in March 13 and the futility was not met. DSMB recommended the continuation of the study. So, enrolment for part two began after DSMB recommendation, that included persons with exposure to face, neck, hand, finger eligible that is high risk exposure within 24 hours in addition to those low risk exposures. And the DCGI permission for enrolment of children was received in August of '13 after submission of data in December, '12. Until then only the adults and post-menopausal women were being enrolled. And then the DCGI permission for enrolment of women of childbearing age was received in April, 2014. And the total enrolment of 200 participants

was completed in December, 2014 and the study participation for the study's participants was completed in March, 15. The primary end point of non-inferiority GMC ratio was met and the data has been submitted for publication. There was no deaths or no PEP failure reported during the 84 day follow up period and based on this, data the marketing authorization approval was received in October, 2016. So, to conclude, a very cautious approach was used for the development, global and local rabies isolates were tested extensively in in vitro assays, demonstrated the direct effect of PEP efficacy in animals, in hamsters models. The preclinical and phase I study data provided the basis for evaluation of RMAb in patients with suspected rabies exposure. Again, initially only the patients with low risk exposures were enrolled and based on the safety and efficacy, then the patients with both high risk and low risk exposures were enrolled. No case of PEP failure or rabies during the study period was reported. Safe and effective monoclonal has been developed

as a passive component of rabies PEP. Thank you.

DR. BIRNKRANT: Thank you very much, that was very helpful that you shared your drug development plan. For the academic perspective, we have invited Dr. Beatriz Quiambao who is the chief of clinical research at the Research Institute for Tropical Medicine in Manila, Philippines where she's a paediatric infectious disease specialist with extensive experience in rabies clinical management and research. She is also a member of the Philippine Department of Health technical working group on rabies and a WHO rabies expert panel.

DR. QUIAMBAO: Good morning. And thank you for inviting me to share with you our experience in the Philippines regarding rabies. So, as a background, the Philippines is an archipelago in Asia that consists of 7,100 islands where 103 million people live. In most of the island rabies, is still an endemic disease. And like most countries in Asia, the dog -- domestic dog remains the principal cause of rabies cases.

And so far we have not seen any rabies among our wildlife, particularly among our bats. Based on the phylogenetic studies, the rabies virus in the Philippines -- I'm sorry, rabies virus in the Philippines is actually distinct from rabies viruses elsewhere in Asia but it's most nearest in origin to the Asian 2a cluster. And even in the Philippines, there are distinct clades for the major islands of Luzon, Visayas, and Mindanao. In 2007, the Rabies Act of 2007 was passed and this mandated the National Rabies Prevention and Control Program which is a multi-agency program headed by the Department of Agriculture in collaboration with the Departments of Health, Local Government, and Education and the components of this program include dog vaccination and registration, stray dog control, information, and education, pre- and post-exposure prophylaxis, and responsible pet ownership. And since then, the program has declared 41 rabies-free islands in the country and these are the colored islands there in the map, but if you will see that -- look at that

number of coloured islands are very small or little compared to the rest of the country. The country sees an average of 233 human rabies cases per year and since 2014, we've seen a slight drop in number of cases and we hope that this will continue to do so. In contrast with the decrease in the number of human rabies cases, we've seen a tremendous rise in the number of animal bite cases and last year, we saw a million patients consulting for animal bites. This is only the number of patients consulting at the government bite centers, this does not consider those that are presenting in the private bite clinics or those who do not consult at all. In the Philippines, post-exposure prophylaxis is provided by what we call animal bite treatment centers and it is represented by the line in red. The number of animal bite treatment centers has increased from 256 back in 2007 and ten years later, it has doubled to almost 500. The goal of the program is to have at least one bite center for every 100,000 population, so to reach 100 million plus

Filipinos, we need 500 more bite centers. Research Institute for Tropical Medicine is a government facility under the Philippine Department of Health and it serves as the research arm of the DoH for infectious and tropical diseases. It contains a 50-bed hospital which is dedicated to the management of patients with infectious and tropical diseases, particularly emerging and re-emerging infectious diseases. It also houses 14 of the 15 national reference laboratories for infectious diseases in the country, and this would include dengue, measles, influenza, TB, et cetera. These national reference labs provide confirmation of these diseases and also QA or NEQAS activities with other labs in the country. The institute also serves as a storage and distribution center for all vaccines for the national immunization program including rabies vaccines and we manufacturer our own purified cobra anti-venom. RITM also serves as a center for training on infectious, tropical, and dermatological diseases. As far as rabies is

concerned, RITM is one of two major government annual bite treatment centers in the country. The other one is San Lazaro Hospital and both are in metro Manila. It is a referral center for the management of human rabies cases and is a rabies laboratory for confirmation of both animal and human rabies. It is also a research center for rabies and we have been conducting clinical trials at RITM since the 1990s. It is an accredited training center for rabies and animal bite management and for laboratory diagnosis of rabies. For animal bite management, we follow the WHO recommendations for PEP, but we have -- just like most countries, we have our own modification and this will include categorizing as category two, wounds that are induced to bleed, because this is quite common in our country. People try to induce wounds to bleed and this sometimes confuses the categorization, so we say that this is category two. And also we are more aggressive in the management of head and neck bites and we consider all head and neck -- exposures in the head and

neck area as category three. We use the Thai Red Cross intradermal regimen and we have been using this since the 1990s. In fact, our institute is the very first one to use the intradermal regimen in the country and -- in 1992 and by 1996 it is already adapted by the national program. So, PEP is provided at RITM into clinics. We have a clinic for the new bites and we see an average of 1,700 new cases every month. 42 percent of these are category three and 40 percent are bites in children. And beginning 2017, the program was already providing equine rabies immunoglobulin free for all category three exposures at our institute, so you will see the tremendous rise in the number of category three patients being seen monthly from about 600 in 2015 and 2016 and just risen to more than a thousand by this year. The other bite clinic is what we call our follow-up clinic where we see an average of 2,400 cases every month. From 2015 we saw, I think, 1,600 a month, 2016, 2,400 cases a month, and now in 2017 reaching almost 4,000 follow up cases every month.

And these patients are given the rabies vaccine complete course for free. RIG is used extensively in our bite clinic and 92 percent of this is given in the form of ERIG. And since we began giving ERIG for free, again you'll see the tremendous rise in the number of those given ERIG. In 2015 and 2016, about 30 percent of patients were given vaccine alone for various reasons, but in 2017 this dropped down to only 17 percent. Completion of the vaccination regimen is quite low, between 56 to 73 percent and the reason for these are values. It used to be the cost, but now since you've been giving it for free, now the people say that if the biting animal is healthy, they don't want to continue the vaccination anymore. Of course, another reason is time constraints, if they work or they go to school, they don't have time to come back to the clinic or they do not like to wait because there is a long line at the bite center, they do not like to wait or they don't like the injection or might be they don't just understand the importance of the timely

completion of vaccination. Our institute also admits human rabies cases and we see about two to three human rabies cases per month, 75 percent of whom are males and 28 percent children. In the past years you will see more children, as much as 40 percent, but right now it's adult male that predominates our human rabies cases. Rabies is clinically diagnosed, although we do take saliva samples for PCR and positivity rate has ranged from 60 to 70 percent and we only give supportive care, we've never tried the (Inaudible) protocol. We've seen our share of PEP failures, these are mostly children with one adult noted in 2014. All of them received vaccine and most of them, except for the first one received immune globulin. The immune globulin was infiltrated around the wound and the rest given intramuscularly. And you can only note that in some of the cases initiation of PEP was delayed as long as two days, but the others received PEP almost immediately within two hours or in the same day of the bite and we don't really know the reason why these patients

eventually came down with rabies. As far as laboratory diagnosis is concerned, we have 20 rabies laboratories all over the country, 19 of these under the Department of Agriculture, and one under the Department of Health. 18 regional and provincial animal disease diagnostic labs are managed by the Central Animal Laboratory at the Department of Agriculture. Only the laboratory at RITM is under the Department of Health and it is the only one that can perform human rabies diagnosis. So, these are the tests that we can do at RITM. We can do FAT, PCR, and ELISA and we also do DRIT for research purposes, as well as RFFIT. We see an average of 200 animal heads -- we test an average of 200 animal heads every year. And we note that the positivity rate has risen from 30 percent to this year as much as 43 percent. In 2008, we conducted a randomized, single-blind, controlled, monocentric trial on the monoclonal cocktail CL184 by Crucell and this is the one that was mentioned earlier by Erin that has been stopped -- the development of which has

been stopped. The objective of the study was to determine the safety and rabies virus neutralizing activity of this monoclonal in comparison with HRIG. So, a simulated rabies post-exposure prophylaxis regimen was used, following the Essen regimen. So, the subjects were divided into two groups, two to one ratio. So, more for CL184, so the CL184 group received the monoclonal plus PVRV using the Essen regimen while the HRIG group received -- also received PRV -- PVRV using the Essen regimen. We enrolled 48 healthy subjects aged five to 18 years old. We initially started with the adolescents and when the DSMB said it was -- there was no safety issue, then we proceeded to enrol the younger children in. And we had two drop-outs during the study by day three because the parents did not want any more of the blood extraction. So, there is also a similar immunogenicity profile between CL184 and HRIG and as far as safety is concerned, it was also similar between the two except that there was more pain in the HRIG group. This study remains unpublished

because the development of this product has also been stopped. So, in conclusion, I'm presenting to you our perspective on rabies and rabies monoclonal antibodies. Whether this -- any monoclonal antibody product will be available to help us attain a rabies-free world by 2030 is up to this group, I guess. Thank you very much.

DR. BIRNKRANT: Thank you very much. I want to thank all of our speakers. We've heard very important information and perspectives that will be essential for further discussion at this meeting. We'll take a 15 minute break, we'll return at 11:20.

(Off the record discussion)

DR. DEMING: Discuss non-clinical and serological models of rabies infection and their uses in anti-rabies product development. First up, we will have Dr. Ellison -- or Dr. James Ellison, who is a microbiologist at the Division of High-Consequence Pathogens and Pathology, have to love that name, within the Poxvirus and Rabies Branch at CDC in Atlanta. Currently, Dr. Ellison

is the technical supervisor for the rabies clinical laboratory where his research interests include the development of animal models for rabies pathogenesis, next generation vaccines, and diagnostic development.

DR. ELLISON: Thank you. I'd like to thank the FDA for organizing this workshop and giving me the opportunity to share some of our work we do at CDC. Just a brief outline of what we're going to talk about today, I'm just going to review rabies pathogenesis and talk about some of the proteins. Then we're going to talk about basic pathogenesis and transmission, experimental rabies, some of the models that were in the past and some of the models in the future, our (Inaudible) model, which is the hamster model for post-exposure prophylaxis and just leave with the summary and conclusions. So, without question, the majority of cases of rabies viruses are acquired from the bite of a rabid animal. That introduction of infectious saliva containing the virus might -- may or may not undergo local

replication in the muscle, but regardless, it will travel along the efferent and afferent nerve axons to the spinal cord, from the spinal cord to the brain where it will disseminate to the exit portals, most notably the salivary glands where the chain of events will continue to the next victim. We're just beginning to understand the breadths of rabies virus variants, especially in the United States. For each species that has been thoroughly investigated, a unique rabies virus variant has been found. The rabies virus is a very small virus, it's only got five proteins, about 12 kilobase genome, and the only external protein is the glycoprotein, and that's what this phylogenetic tree is constructed from. This is some of our work that includes about 600 full-length glycoprotein sequences. In general, rabies can be divided into two major clades, one associated with bats and the others with carnivores. The glycoprotein is critical because it's the only exterior antigen, so it's the only one that's going to produce virus-neutralizing

antibodies. There's four epitopes that are minor site a that are along this glycoprotein and the majority of natural infections -- naturally infected animals have antibodies directed against site II and III, which one's a linear epitope and the other's a conformational. So, the history of animal bodies in rabies research really started a long time ago in 1804 when Zinke took a small brush and swabbed the mouth of a rabid animal and introduced that into the hind of a -- the hind limb of a dachshund into wounds that he made and this basically showed that rabies could be passed experimentally. It wasn't until Pasteur's studies in the early 1800s that demonstrated rabies could be experimentally transmitted from animal to animal and this is what really facilitated further studies in pathogenesis diagnosis and how the first rabies vaccine was actually invented. Most of what we know about the events that take place during a rabies infection has been learned from experimental models. Everything from dogs, rabbits, cats, hamsters, foxes, non-human

primates, over the years at CDC we've used skunks, foxes, raccoons, bats, non-human primates. But all these studies further our understanding of the pathogenesis that occurs during rabies. In terms of incubation period, one of the most robust studies to examine incubation period took place in the 90s with the striped skunk using a skunk virus -- a skunk street virus. You'll hear this term street virus thrown around and what that basically means is that's a non-laboratory strain, so you've heard CVS-11 this morning, that's a laboratory-adapted strain challenge virus standard, and this street virus is just a isolate that was derived from the infected animal. So, we've got a homologous host with a homologous virus. And what they did was they used a really sensitive PCR technique to investigate whether virus is replicating in the local muscle or not. So, after they did their PCR, they actually looked by IHC prior to the development of clinical disease and what that showed us was that there was evidence of infection of the extrafusal muscle fibers and

occasional fibrocytes at the site of infection. Although it was unclear, the infection of muscle fibres may be a critical pathogenic step for the virus to gain access to the peripheral nervous system, such is why we infuse immune globulin into the wound site. So, for biological and medical products for animal models, WHO recommends that in addition to in vitro testing of RIG and other products to determine the neutralizing potential and some measure of expected efficacy is desirable in vivo. Reproducible animal models should be used for assessing the effectiveness of medical products for in situ virus neutralization after infection. The in vivo half-lives of antibody preparations in relevant target tissues should be established for new preparations. The level of antibody required for passive immunization and the duration should be determined, particularly for those based on human monoclonal antibodies. There are some faults and problems with any experimental model, this can occur from a reproducible challenge. There is substantial variation and

mortality by species and even strains within species, so certain mice show different mortality compared to others. There is an out-bred versus inbred animals and it doesn't actually replicate human disease exactly. We've talked a lot about rodent models. There's actually no rodent model in nature, there's no reservoir in nature for rabies virus. So, these are non-target animals. Differences in heterologous and homologous infections could be influenced by the species barrier. For example, if you take raccoons and you use raccoon virus in them, you can have 100 percent mortality. However, if you use the raccoon variant in hamsters it's only 30 percent mortality. There's also cost and ethical considerations, dogs are companion animals that are highly scrutinized. Non-human primates, you might not be able to get the sample size you need. I wouldn't want to work with 300 rhesus macaques at a time. So, what we've really used and developed at CDC is the hamster model. The hamster model has been used as a standard to

evaluate PEP regimes. In the early studies post-exposure prophylaxis hamsters were found to be extremely sensitive to rabies virus challenge and demonstrated a more reproducible attack rate than other rodent or non-human primate models. High attack rates observed after intramuscular injection of a large viral inoculum in rabies vaccine is unable to provide complete protection thus facilitating use of the hamster system as a model of severe human exposures to rabies virus. So, using the hamster model, we are able to effectively reproduce incubation, clinical signs, and the failure of vaccine alone to prevent the majority of rabies cases with certain isolates. And this is just a schematic of the hamster showing you -- the red dot represents where the infection and the site of immune globulin is introduced, that's the (Inaudible) and pathogenesis studies over the years have determined that from the site of inoculation the virus transmits through neuronal retrograde viral transport at about 50 to 100 millimetres per day.

So, the greatest utility of the hamster model is the ability to evaluate the passive antibody component in PEP. When experimentally infected, the mortality rates in hamsters treated with vaccine alone approach those of untreated controls which is about 80 to 100 percent. When passive immune globulin is given in addition to vaccine, the survival rates are about 70 to 100 percent. And what this does is demonstrates an effective contribution of the passive immune globulin distinct from rabies vaccine. The efficacy of the immune serum plus rabies vaccine in the hamster model is similar to that observed in the few human clinical investigations evaluating the combination of both serum and vaccine. We've talked extensively about the Iranian study this morning, so I won't belabour that. But given the added contribution of passive antibody was only demonstrated in the most severely exposed people, an animal model to evaluate the passive component of PEP should be sufficiently rigorous. The vaccine alone is unable to prevent disease. So,

just in summary, a well characterized animal model is essential to evaluate any proposed anti-rabies biologic intended for use in PEP's regimes. The global breadth of rabies virus variants must be considered when evaluating new animal models, and the hamster model shows great potential in addressing many confounding factors associated with other animal models in PEP evaluation. I'd like to thank you for your time.

DR. DEMING: Thank you Dr. Ellison. Is this on? Yeah. I think it's on. All right, next we will hear from Dr. Susan Moore who is currently the director of the rabies laboratory and a clinical assistant professor at the Kansas State University, College of Veterinary Medicine. Her research interests are laboratory methods to detect and measure vaccine response and response to infectious diseases with a primary interest in rabies. Rabies epidemiology and public health efforts to combat infectious disease is an additional area of focus. Thank you.

DR. MOORE: Thank you. And I'm happy to

here to be talking about rabies serology. A lot of the results we looked at in the previous talks of serology data was presented, and I think it's important that we know the capabilities of serology, and also the limitations of serology when we're looking at these results. So, to get started, rabies virus neutralizing antibodies which are -- have been shown to be the major component of protection from rabies. And so that's very why we measure them. We do it for several different reasons, primarily to show that there has been a proof of the response from vaccination. And that includes clinical trials, it also includes diagnostic samples. Diagnostic samples are -- in the United States are evaluated only at the CDC. At Kansas State, we may look at serum and see if CSF -- if -- only if they're trying to rule out rabies. But we also measure for vaccine response in all kinds of animals, dogs, cats, ferrets, domestic animals, zoo animals, for travel, and for research product development, and also field sero surveys. I

mention all these different reasons because serology, the method that you choose, sometimes depends on what the purpose of the testing is and may vary a little bit. Because we are using rabies serology as a tool to look at the effectiveness of vaccination, we need to understand how the serology is correlated to protection. And as other speakers have done, I wanted to look at history. We look at animal models, so in dog and cat trials you can actually look at serology compared to survival. And this is a true definition of determination, of protection, something we can't do in human testing. One of the earliest studies by (Inaudible) in 1984 used a statistical model, a probit analysis, to look at the titers from the serology testing and predict the probability of death. What they determined was at titers of about one to 30 or by mouse neutralization test or one to 44 by RFFIT, the probability of deaths was about one percent. And then later Dr. Aubert, in 1992, published a paper where he summarized a lot

of different challenge studies. And what he determined was in cats, the effective level, which showed protection, was 0.1 and in dogs was 0.2. So, I just kind of wanted to show this figure from the Bon and Ridpath (ph) paper, and unfortunately I cut off -- I thought this was an open box, so sorry about that, but I wanted to show this because it showed how the percent, the death rate falls as the titer level goes up. And when you get down to what was supposed to be in the box, the one percent chance of death is that titer of one to 30 by the mouse neutralization test and one to 44 by the RFFIT. And that he actually got it down to a 0.1 percent chance of death, and at that level it was about a titer of one to 100 both for the mouse neutralization test and the RFFIT. So, this shows that the higher that the antibody level gets, the probability of death goes down, up into a certain point. So, if a titer of one to 100 is approximately equal to an international unit per mL of one, so, when you see these results of 20 international units or 100 international units per

mL, you know that that's well above what these animal studies showed was protective level. The other thing that came out in the Aubert paper was that even though the 0.1 and the 0.2 were effective levels determined in cats and dogs, based on the variability of the assay he recommended that the level be determined -- or be set at 0.5, just so that it was robust enough. And that's where the 0.5 comes from, is from animal studies. So, for humans obviously, we can't do any challenge studies, and so this level was actually independently determined from looking at the results of vaccine clinical trials in, like, the 1950s to 1970s. So a group got together in 1970s and looked at a whole bunch of results from vaccine clinical trials and determined that the level should be 0.5 for a sample that was collected four weeks after vaccination, and that would be determined if you're at 0.5, shows that you had an adequate vaccine response. There are actually two guidelines that give these recommendations. The World Health Organization

uses the 0.5 where the Advisory Committee on Immunization Practises in the United States gives the level as complete neutralization of rabies at a 1.5 serum dilution in the RFFIT test, which is approximately equal to 0.1 IU/mL. So, then that comes to the question, what level is significant? Are we saying what level is significant for protection? Most people would say that's what we want to look at, or is it what level means they're sero-converted. Does it matter whether there's different exposure levels? Do we want to say you have to have a higher level if it's severe exposure or a lower level of less exposure? Does it matter whether it's a different rabies strain, some -- for some of the lyssaviruses like EBL-1 and 2, I think the recommendations are to have a considerably higher rabies serology result, should be determined adequate. Does the same level apply for all situations? All vaccination statuses, age, health? Does this 0.5, 0.1, apply to all serologic methods? Time since vaccination, does it matter -- are we just measuring it four weeks

after vaccination, are we measuring it right before challenge, right after challenge, what are we looking at here? And what is more important, your vaccination status or your rabies antibody level? So, I'm just -- the rest of the talk I'm going to concentrate on rabies serology for people who aren't familiar with the different methods, primarily the -- it all started with the mouse neutralization test, and that was the gold standard for many, many years. And then the RFFIT, the rapid fluorescent focus inhibition test, was developed in 1973 by Jean Smith at CDC, and it was published and it was used in parallel with the mouse neutralization test for several years before it was -- most people converted over to using the RFFIT. In 1991, Jean Smith published what I considered a QA guideline, which I thought was very important because it is a variable assay, it's a serum neutralization assay, and it was published in the WHO methods manual in 1996. The FAVN test was developed around the end of the 1990s, and the reason -- so it stands for

fluorescent antibody virus neutralization test, and the reason it was developed was from the time the RFFIT got put in use up until the 1990s, a number of laboratories doing rabies work modified the RFFIT. And every time an assay is modified, you can change the performance characteristics of it. And so when someone said they were doing a RFFIT, and another person said they were doing a RFFIT, the results may be slightly different because of the modifications they had made to their method. So, the group in Nancy, France, the AFSSA laboratory developed the FAVN primarily for pet export, because they wanted an assay that could be very much standardized and used throughout the world and everybody would be using it the same way, and the performance characteristics would be exactly the same. It's really a modification of the RFFIT. It's done on 96-well plates. There are some other minor differences, but essentially it's a serum neutralization test like the RFFIT. The only difference, I would say, is that it promotes

standardization, and people who are doing the FAVN for pet travel have to participate in a proficiency testing program, which means that their results are comparable to other laboratories that are doing FAVN testing. There is the ELISA test, and there's several different types. There's competitive ELISA, there's blocking ELISA, there's indirect ELISA. Each of these methods have their advantages and disadvantages. One of the advantages of some of the modern ELISAs is that they are kits. Again, this aids in standardization and reproducibility of results. The downside of ELISAs is many of them only measure binding antibodies and not strictly neutralizing antibodies, and so the comparison between an ELISA result and a serum neutralization result like from a RFFIT may not be the same. So, this is just a diagram that shows how the serum neutralization test is done where the serum sample that may contain rabies neutralizing antibody is mixed with viable rabies virus, and if the neutralizing antibody is present, then it will

neutralize the virus in the well of the slide, and then you add tissue culture cells, so if there is any non-neutralized virus, it will infect the cells and it will reproduce, and then you stain that with a labelled anti-rabies N antibody that's conjugated to FITC, so you can visualize the virus that's growing in the cells and then you read that. So, if there is virus present and neutralized all the virus, you won't see anything on the slide as far as FITC, and then if there is no antibody present, you will see the virus growing in cells. Where ELISA is -- this is an indirect ELISA where you add the serum sample to the plate well that has the antigen on it and then you visualize it with an enzyme reaction. And this is just a schematic. If anybody is interested, you can look at it on all the different steps. The reason I include this is it is a very manual method, it takes -- for RFFIT, there is a 24-hour incubation period, for FAVN, there's a 48 hour. It's a manual read-out of using a florescent microscope, though there are

some methods being developed where the reading can be automated, but for the most part it is a manual method. And this is the reading of -- like I mentioned before, you're going to see virus or you're not going to see virus and then you count the wells, and those counts are then put into a formula for in-point titer (Inaudible) to get the titer value. But controls need to be included if you want to make sure you're maintaining your performance characteristics. I want to mention that each assay should include the WHO reference standard. As was mentioned previously, the first WHO standard was an ERIG product, and then the first WHO human standard was made in the 1970s and that was 59 IUs/mL and then the second in the 1990s which is 30 IUs/mL. The reason I want to mention this is the first one, the 59 IUs in our laboratory, we have noticed over several years -- we've been evaluating both products since 2005. That the first one has lost some potency and so we no longer use it, we still test it to compare it against it. But it has -- in our hands, it's not

anymore 59 IUs, and so we strictly use the WHO to SRIG standard, and so I just wanted to mention that sometimes that can make a difference. Internal controls are important to make sure you maintain your repeatability and your reproducibility. The virus control is important for the RFFIT, the target dose is 50 TCID50, and for the FAVN it's 100 TCID50, and then you have your cell control. So, once you get your titer value, you convert that into international units per mL by dividing it by the titer of the reference serum. So, it's a simple calculation of the titer of your test serum divided by the titer of your WHO reference serum, and then you multiply it by the potency that's used. In RFFIT, that's typically a 2 IU potency level for the standard. So, depending on what you're doing it for, like I mentioned before, you may have a high need for precision. If you're doing product testing, you need to make sure that the RFFIT or sero-neutralization test that you're using has a very high precision and repeatability. If you're doing

it for screening, it may not need to have a high precision. So, it depends on if you were looking at the specificity of the response, and you want to make sure that the vaccine responds -- the specificity of it is targeted to the strain that the person is going to be exposed to. If you're doing testing for bioequivalence biologics, the requirements for validation are very high FDA requirements, the ICH requirements. So, the validation, what -- the validation that you do must fit what the purpose is. If you are modifying the assay, which you can, whether it's a neutralization assay or an antigen-binding assay such as an ELISA, you can modify any of these assays to particularly look at specificities, so you could change the strain of the challenge virus in the test. You can change the linear range of your assay by changing the dose of the challenge virus, increasing it or decreasing it, and these are just another number of ways that you can modify the assay to make it more fit for your purpose. I wanted to bring this up in particular

because for monoclonal testing, if you're looking at different specificities, you need to change the strain of your challenge virus so you can make sure that when you're doing the serology testing, that you're covering the breadth of that monoclonal. And the same thing can be said of antigen binding assays, so if you want to make -- look at the specificity of the binding antibodies that are made, or the binding capacity of the monoclonal, you can change the virus strain of the antigen on the plate. And since we're talking about monoclonals here, I wanted to mention some challenges that we have faced in the laboratory of measuring monoclonal antibodies, is when you're looking at the specificity and you're changing the challenge virus strain in the assay, that means you need to grow that virus up, that wild-type virus up to sufficient quantity to serve in that assay, and that can be a bit challenging because many of the wild-type strains don't grow as easily as the lab -- obviously as the lab-adapted strains. And then for unit of reporting, normally

rabies serology results are reported as international units per mL or for ELISA, equivalent units per mL, but for monoclonals where we know the actual concentration, sometimes it makes sense to report them in micrograms per mL, and how does that relate to, you know, the historical results of international units per mL. And sometimes you need to, if it's a cocktail of monoclonals, like two monoclonals together, you may need to assess and differentiate between the mAbs and clinical samples, and you need to adapt your serological assays to be able to do that. And that's all I have, thank you.

DR. DEMING: All right, thank you Dr. Moore. Okay, so as we've heard this morning and we will continue to hear into this afternoon, is that there are several challenges and probably limitations to clinical efficacy studies. For example, efficacy data for many prophylaxis study is going to be limited to the diversity of the rabies viruses that are endemic to the study sites. So, what we're going to discuss in this

session hopefully is what can we learn from the non-clinical and serological type models to support clinical data. And the way we'll handle this is I'll run through a question, we'll have a discussion between the panelists and then I'll open it up to the audience in general, and move on to the next question, so forth, then hopefully we'll be done in time for lunch. Okay, so the first question is what can be learned from different animal models about the potential contribution of monoclonal antibody products? Keeping in mind issues such as the breadth of coverage against diverse rabies virus strains, the potential for rabies virus to escape neutralization, the contribution of the rabies virus monoclonal antibody product to PEP activity, the contribution of individual monoclonal antibodies in a monoclonal antibody cocktail to PEP activity and the selection -- what can we learn about these -- we're using these models to inform the selection of monoclonal antibody dosing regimens for the initial clinical evaluations.

We'll just open it up to any panelist interested contributing. Okay, well, several of these issues were covered in the talks. One thing that might be worth discussing is, in the case of a cocktail where we have two or more monoclonal antibodies, it is necessary to demonstrate that each is contributing to the overall effect. Using an animal model, for example, is it possible to actually test various rabies virus strains where it might be less susceptible to one monoclonal versus the other, or perhaps to neither? Just to verify that there might actually be some sort of a quantifiable effect?

DR. FEHLNER-GARDINER: Maybe I can start. My name is Christine Fehlner-Gardiner, I'm from the Canadian Food Inspection Agency, Rabies Lab. And maybe I'll just mention for the panelists when you do present your question or your comment, to please introduce yourself each time you speak for our transcriptionist. That -- what you just described is actually quite standard in the case of mon -- testing different monoclonal antibodies,

that they would be tested individually as well as in combination to look at the neutralizing potency of the individuals and the cocktail. And certainly some of the work that we've done in collaboration with a company that's producing a potential product has shown that not always do each of the monoclonal antibodies neutralize all of the variants that are tested, but what we're looking for is that in the combination, do we seek complete coverage? And so that's an important thing to be looking for, that if you're not -- if you're going to use a single monoclonal antibody, then that has to have complete coverage. But one of the advantages of using a cocktail is that you can have the combination that will have complete coverage.

DR. DEMING: I don't think I told my name. My name is Damon Deming (ph), I'm with the Division of (Inaudible) Products, but -- so in that case where you only have one monoclonal that is presumably effective against the challenge strain, are these models sensitive to the

potential for the selection of resistance, I mean relative to, like, the polyclonal RIG products? Do you think that that would be a concern, and if so, would these models adequately cover that?

DR. FEHLNER-GARDINER: Perhaps Dr. (Inaudible), would you like to comment on that? Oh, sorry.

DR. MOLRINE: (Inaudible) I'm not -- oh, there we go, thank you. That the -- I think the hamster model is the most established model for looking at the post-exposure prophylaxis. I guess, you know, the question is, how much one does if one is going to be looking at 28 different strains that you've done in your RFFIT, would you need to actually do that, you know, all in your animal studies, which I think most is cost prohibitive, you can't do that. So, I do think you have to take -- use your RFFIT data, you know, and look at for the different strains that you're looking at, if you have more than one antibody, how the two of them may neutralize in that in vitro system, and then potentially if you're going

forward with a cocktail. If that's going to be your product, you know, how much you'd have to look at each individually versus the cocktail, because that is your product in the animal system. So, I think that, you know, is a challenge, if the expectation is that for many different variants in the PEP model, that you'd have to be looking at each individual component versus potentially if your product is more than one, that you show that in vivo, which is your product that's going to -- that effects, you know, is potent against the strain. So, in terms of escape neutralization, you know, I think that's really maybe some of our animal virologists, you know, can comment on that. I mean, to -- I'm not sure the PEP model in terms of how fast the virus, you know, gets into the CNS and works, if you're going to be able to do experiments to take that, you know, passive component repeatedly, and show that. Certainly I think in the laboratory people do pass the rabies virus in different cell culture and you can look for that. But I'm not sure about in the animal

model.

DR. FU: Is it working? I think the animal model in terms of (Inaudible) testing individual monoclonals with different viruses, a mouse would do a good job. But without a PEP, you know, just testing. With a PEP, definitely the hamster would be much better. In terms of mutation, an indi -- of course, preferably a cocktail would be better, it would prevent a possible, you know, escape by one so the other one can take care of it. I think the Crucell has shown with, you know, one of the previous presentations has shown that. With the individuals, I'm not too sure, one of the companies, they show that a single antibody can almost protect against all the isolates they tested. Of course, with a single one, there's always a possibility of an escape. But to my own thinking, the escape is very unlikely. Rabies viruses, unlike many other viruses, because of the exclusive neurotropism, you see we are talking about all the (Inaudible), they are highly

mutable, so therefore we see a lot of variants. But the way the rabies (Inaudible) variability comparatively, I think one of the reasons possibly against to do most of the mutants are lethal, are actually not survivable in the animal system. So, that's my own taken by (Inaudible) of the studies. Because we tried the in vitro to mutate the virus, we can mutate the virus very easily, we can do passing a cell culture for many times without going back. But if injected animals, it just take about -- maybe one passage, the virus will mutated back to its own. It doesn't matter how you do it. It's very strange, I think that that's -- my own thinking, it is a man of the mutants, sort of a (Inaudible) mutants, they're not going to survive. Sorry, I'm Zhen Fu from the University of Georgia.

DR. ELLISON: Yeah, and I just wanted to say, if we did have an evidence of escape in the hamster model, we would sequence that glycoprotein, and you could see the evidence of mutation and in that specific epitope. So, if there is an escape, for instance, in the hamster

model, we would confirm it by DFA to show that it is rabid and then we would sequence the glycoprotein of the particular virus recovered from the CNS of that animal. And there you can look to see if there was a mutation in that epitope.

DR. DEMING: And you haven't seen that in animals that did succumb to infection even with monoclonal ---

DR. ELLISON: Not based on our previous experiments, but we do see that you can induce artificial mutations through laboratory adapting and passaging it in cell culture.

DR. TAYLOR: I think it's perhaps relevant at this point just to point out when we're talking about evolution of escaped mutants that we're talking about human productive use in humans, those are dead end hosts. That virus that escapes that in that person is not going to go anywhere. So, I think, you know, if you were applying this product in a reservoir host situation, you would worry about that. But this

is -- in the dead end host, I think that is far less of a concern.

DR. DEMING: Well, we're concerned about, you know, it's -- as far as I know, the heterogeneity of the viral (Inaudible) from a (Inaudible) biting animal and its saliva isn't quite clear. We'd just like to make sure we have coverage of that, because even if the virus isn't going to go from a person, if they develop rabies, (2:59:08.9).

DR. CONNELLY: (Inaudible). So, I'd like to invite further discussion about a point that Dr. Molrine brought up, and it's that there is the approach, you know, you can just test a single strain in one animal and then there's testing every single strain in animals, which has a lot of challenges to go into that. So, something in the middle, if you were to select more than one strain to test, just -- I'd like to invite discussion about potentially selecting ones that might be particular to certain geographic regions where trials may be considered or in the case of a

monoclonal cocktail, discussion about ones where maybe only one component of the cocktail in the in-vitro testing has coverage and another doesn't. So, if you are trying to, in an animal model setting, be thoughtful about what viruses to study, how would those decisions be made.

DR. FRANKA: If I may comment, Richard Franka, CDC. So, we -- in the past ten years, we have done many, many experiments, and I think it was mentioned already before by Debbie and Christina that there is a stage approach, you started screening many different viruses, but as a few of the presenters have mentioned, there are different groups and lineages of viruses and some of them are similar and some of them are different. So, what you start to do is select based on different geographical regions, but also from different lineages, and you screen those in vitro with both -- with two, three, or four, how many monoclonals you have, and based on the results of these -- of this testing exactly as you mentioned, you select those -- especially those

which are not neutralized by one monoclonal antibody and after you use those in vivo system in hamster model -- on other models, as well. And this will decrease the -- not only cause, but also all the resources needed for testing of all viruses. Challenge becomes which geographical regions to select before testing, before licensure, before approval and after, how to continue surveillance post-marketing to make sure that if there are new variants which may not be neutralized by one or two antibodies, that those are actually captured and who should be responsible for those. Thank you.

DR. FEHLNER-GARDINER: If I could just add another comment, that perhaps in the selection of those particular variants, that the epitope against which the monoclonal is directed is known for these products, and so I think it would be important to look at diversity of viruses within that sequence of the important residues within the epitope. So, if you only were to select a few viruses to look at in your animal model, that you

want to look at ones that very different within that particular epitope, even if they may be within the same (Inaudible) within phylogenetic tree. The important part is the epitope for those monoclonals.

DR. FRANKA: Just add one point, and this was -- this is -- I forgot that -- (Inaudible) you can actually predict based on sequence of the epitope, which would be neutralized by antibody or it will not be neutralized. So, you can predict it without even doing testing, and after you just confirm it in vivo -- in vitro (Inaudible) in vivo.

DR. DEMING: Even though it's a little more difficult for the -- when the epitope is non-contiguous to predict.

DR. FRANKA: Yes, that's true. That's true.

DR. BIRNKRANT: I have a question. Is -- I'm sorry, you want to go first?

DR. DEMING: Go ahead.

DR. BIRNKRANT: I was wondering if wound

cleansing is part of the animal model, and if not, how do we best relay the results from the animal models to have confidence to go, then, into human studies?

DR. WILDE: That's a difficult question to answer for me, and I think for most of you, because wound cleansing is not done in any consistent way. They don't even, you know, use the same substances. The WHO and people like myself in our group, we just recommend soapy water, which seems to work very well. But whether or not this affects mutations or has any genetic impact, I really have no answer for that. It's just extremely important, because 40 percent of human deaths can be reduced just by adequate wound cleansing, but then what is adequate wound cleaning? It's so individual on top of not just using whatever substances used.

DR. FU: But I think one thing in human's and animal bites, in animal models, we injected them, so here's no way you can wash them out anyway.

DR. ELLISON: I think that's an important part. We aren't simulating it by infusing them with virus and definitely, at least in CDCs animal models, (Inaudible) wound cleansing is not even possible.

DR. BLANTON: I mean, I would just add to that, it's also in terms of being an extremely lethal dose of virus that's injected, so that's probably not necessarily representative of the majority of bites that would occur in major ---

DR. WILDE: We don't even have any consistent reports on the microflora of dogs. I think my group has tried to do some study of (Inaudible) dogs, or dog carcasses, as soon possible and the publications are confusing. We haven't even decided in committee meetings what is a normal antibiotic that should be used, you know, as an empirical antibiotic, there are no recommendations. And amoxicillin is what everybody uses, but there are no scientific studies to really confirm that that's correct. Now, in cats, pasteurella multocida is of course

almost in every cat and it's an extremely virulent organism (Inaudible). You know, you see kids -- patients coming in with a full blown cellulitis within five or six hours. So, there's a lot we don't know. You know, that's the whole problem about all this. This is different than, you know, dealing with pneumonia or dealing with polio or some new Zika virus. We just know even less about the basics in rabies. The clues that you have to make a determination for treatment are not easy, you know, there are very few of them. A lot of it is (Inaudible) and experience and tradition plays an extremely big role in rabies. You know, try and change rules. You guys are going to experience all of this now.

DR. NELSON: Skip Nelson, Office of Pediatric Therapeutics, FDA. I have a question. In terms of the hamster model, what happens if you just use immunoglobulin alone and no vaccine?

DR. WILDE: Well, they tell me that -- your friends at the CDC a long time ago, told me that you prolong deaths, that's all. Whether

that's still true, I don't know.

DR. BIRNKRANT: We ---

DR. WILDE: Well, (Inaudible) published that.

DR. FRANKA: Yeah, it -- so, yeah, actually protects majority of animals. But in some cases there one -- let's say if you have ten experimental animals, most of the time it protects just immunoglobulin by itself. If given in a timely manner and into the wounds, but in ---

DR. WILDE: And this has been substantially published in good studies.

DR. FRANKA: It -- yeah, it was good study, yes. And only challenges that in some cases, we observed maybe five or ten percent of animal -- essentially from (Inaudible) animal, sometimes developed rabies much later in the study. But majority of them survived.

DR. WILDE: That's extremely reassuring. You know, I ---

DR. FRANKA: Yeah, and it's simple experiment to do.

DR. WILDE: Yeah.

DR. DEMING: Okay, so it seems that the hamster model is the most developed, but are there situations where it make sense to use another animal model to answer any specific question or as a follow up?

DR. FRANKA: You know, I think hamster -- in our experience at CDC, we use hamster model very often. There is a lot of data supporting the information we get from using different variables. It provides substantial data that we can essentially assess vaccines or monoclonal antibodies. In a similar way, we have a lot of different viruses (Inaudible) to this model, which as just mentioned is severe infection model. It's not your usual animal bite to humans. This is set up in a way that we have 100 percent mortality in a controlled group and this way, we can measure if there is any added benefit of vaccine, vaccine and combination of antibody. So, hamster model is sufficient in my opinion. There were cases when we did testing in non-human primates and those was

-- those were mostly because of a request for some animal model which is closest to humans, but as it was mentioned in some of the presentations, sensitive -- rabies is 100 percent fatal when symptoms developed. But not everybody gets rabies after being bitten by rabid animal. So, that's other challenge we should be taking into account when you look into clinical trials. You may even test animal, as Henry mentioned before, (Inaudible) of virus in saliva is intermittent. So, animal could be rabid, but the virus is not in saliva, and even if there is virus, not everybody develop rabies.

DR. DEMING: Just as a follow up to that, I'm jumping a little bit ahead here to number 3. Is there or would there be an animal model that would actually allow you to assess the risks associated with interference with vaccine response? So, clearly with a hamster model, the vaccine contributes little to nothing. But if you actually wanted to measure that inhibition, would there be a model that you could do that?

DR. FRANKA: It could be possible. I don't think we ever really look into it, but as the discussion goes, there may be other (Inaudible). If there are two models that you can measure efficacy in animal model, and if you want to look into interference, it could be done in clinical trials. I'm not sure in animal model, but maybe ---

DR. FU: Because the rabies vaccine is an (Inaudible) vaccines. So, the antibody interference is minimal.

DR. LEVIS: All right. Sorry, Robin Levis, I'm in the Division of Viral Products at CBER. And I would just ask Richard, or someone from CDC, I was interested in your comment about the comparison with the non-human primate, because as we review things, we're trying to look for the best models, and could you just talk in a little bit more detail about any utility to the nine human primate model versus the hamster model in terms of going forward?

DR. FRANKA: Yes. So, different animal

species have different susceptibility to rabies, and hamster model is really susceptible to many different viruses. That's why we use it as a standard. We did few experiments, very few in non-human primates and in very -- with very small sample size, and in some of those experiments, it seems that they -- we didn't test in so many different viruses, so challenge is caused for those tests, and also sensitivity or susceptibility of the species to different viruses, which are unknown. So, this is the challenge, but it seems, based on some rare studies in non-human primates that their, you know, susceptibility is much lower than in hamsters which is in some way similar to humans.

DR. MOLRINE: I think -- this is Deb Molrine again. I think that the pet model can be used to look at what dose of your passive component might interfere with your vaccine, and so you look at -- so I guess you're wanting to look at it in two ways, just in terms of protection, right? So, you initially might have

your -- you know, your HRIG will have as the control of your different doses of mAb and give that with vaccine, and you'll probably see a differential effect of protection, which is either going to be to (Inaudible) not enough passive component and we're relying on your vaccine only. Potentially, you could give two (Inaudible) of passive component and then interfere with the vaccine response. I do think that's harder in the hamster model, because I do think that initial protection, you know, from day -- around day three to seven is, like, really important. But, you know, you can measure serology in these animals and looking at different doses of your passive component and how it affects your vaccine. So -- and I think you will see a differential effect, but potentially, the challenge is more that -- in that model, because it's such a severe infection, the initial protection by your passive component is very important.

DR. LEVIS: Thank you.

DR. FRANKA: Thanks. Hi.

DR. SRINIVAS: Hi. Geetha Srinivas, I'm from the CVB, Center for Veterinary Biologics. There is some work going on with regard to the natural host being canines -- dogs. So, to use the PED in dogs, this is mainly for shipment of dogs or import and export of dogs. Some work is being done and there they do have to show lack of interference for (Inaudible) vaccine. So, there will be multiple doses that will be used and it has to show susceptibility or protection against different strains of the virus.

DR. FRANKA: Thank you.

DR. CONNELLY: I just want to follow up on one comment that was said about the ongoing surveillance for the various rabies virus strains, and could somebody potentially from CDC just educate us a little bit more about how that is conducted? We heard from Louise Taylor this morning, certain geographic areas might have different abilities to conduct surveillance, and so I'd just like to understand how representatives' surveillance efforts are to

categorize the various strains.

DR. BLANTON: Yeah, this is Jesse Blanton from CDC. So, we actively, as the (Inaudible) for the US (Inaudible), about 120,000 animals are tested for rabies each year by our laboratories in the States. From those, we generally work to have representative samples from all the positives sent to CDC for further characterization. As Louise presented, this generally involves very targeted antigenic molecular type (Inaudible) specific species or (Inaudible) working to improve the sort of guidelines for which samples are sent for further characterization. And this is something we actually had some discussion about, I think, ten or so years ago, back when we first started doing some of the monoclonal (Inaudible) this product become available, setting very specific guidelines about routine sampling and typing and molecular characterization of viruses that are in circulation in the United States. I'm looking at it on kind of an ongoing basis for potential, you know, variants that may not be covered by any

licensed (Inaudible) agents that will be available.

DR. BELL: Can I ask in the international setting, if the same degree of expertise available, if anyone, on the panel would happen to know, for example, maybe India or the Philippines?

DR. FRANKA: Probably not, you know, and -- I'm sorry, I'm jumping, but just from presentation, how -- you know, the rabies is in developing countries where they don't have laboratories and they cannot do sequencing and -- so, before you ask question, I was just going to comment that if it's (Inaudible) US citizen or people bitten overseas coming to United States, this has to be taken into consideration if there are different variants involved, yeah.

DR. WILDE: Well, you know, if you see a lot of rabies patients over the years, you know, we have seen close to 140 now that we've been involved in clinically, you know. A significant number, you know, an impressive number, I can't give you a percentage, but maybe guessing, like,

five or ten of these had completely atypical presentations. You know, for example, I've seen one patient that came in with status epilepticus. I've seen another patient that came in with a ruptured esophagus, you know, from -- presumably, from vomiting. Often the histories are inadequate, but even if you have a history, there's a significant number of patients worldwide. For example, one of the survivor's, the child from a cat bite in California, had non-neutralizing antibodies and also very atypical presentation. You have, you know, any way of identifying these and you know, sequencing them and (3:19:29.5), but have sequenced some and found not much difference, you know, something unusual. We we have good sequencing capabilities in Bangkok in our virology group that works with us, and we also identified, for example, the mystery between why do some have paralytic rabies and why encephalitic rabies. You know, the thing that alerted us that there's a mystery there was that we had one patient that got bitten by one and the

same dog and one had paralytic rabies and the other one had encephalitic rabies. After that point, a lot of people believed that this is a different, you know, type of virus with different variants and it wasn't. So -- and now we know that it's an immune response of the host that makes a difference between paralytic, and this is published, and -- but some of the real strange presentations are curious, and do you have -- done any effort -- efforts at CDC, you know, to try and identify and look at them more closely, real bizarre cases?

DR. FRANKA: You mean in humans or ---

DR. WILDE: In humans, yeah. (Inaudible).

DR. FRANKA: Not necessarily. We provide supporting laboratory testing for human cases in United States, but they are rare and we didn't go into details of different...

DR. WILDE: They don't alert you, too, probably.

DR. FRANKA: Yes.

DR. WILDE: They don't say this is a crazy case, you know, (Inaudible) or whatever, or have unusual neurological symptoms. For example, we've seen one that had a localized paralysis (0:37:04.5) and that's what that patient presented and, you know, atypical laboratory findings of rabies.

DR. FRANKA: Yes. We didn't look in different presentations...

DR. WILDE: No.

DR. DEMING: All right, we're going to -- we're running low on time here, apologies to the audience. I'm going to go ahead and combine two or three -- but I'm sorry, do you have a question?

DR. SIBERRY: Yes.

DR. DEMING: Yes.

DR. SIBERRY: Thanks very much. George Siberry, State Department PEPFAR Program. I heard Zhen say something that I think is really critical. I heard you say you're not worried about interfering with the response to the vaccine, because it's a killed vaccine, and that

really is a critical part of a lot of the questions and designs here. So, I want to challenge you a little on that to see if there's consensus for your statement, because it seems to me that would have a tremendous impact on the way forward.

DR. FU: Well, that's what I think ---

DR. SIBERRY: Do you want to have...

DR. FU: If you think otherwise, please.

DR. SRINIVAS: Lack of interference is a big aspect of the study, whether it's live or killed (Inaudible) at least in the veterinary vaccines. We have seen interference by components other than the (Inaudible).

DR. DEMING: All right, that's a component of the next question. So, I'm just going to go ahead and present those. I'm actually just going to combine 2 and 3 because I think 3 (A) covers 2 well enough, so I'll just read 3. "How can animal data, which we've talked about quite a bit, and serological data from trials enrolling non-rabies exposed healthy volunteers

help to support initiation clinical trials in suspected rabies virus exposure, considering issues such as breadth and initial time (Inaudible) after antibody administrations of that window phase? Later effects of monoclonal antibodies on vaccine response, which we consider (Inaudible) when we're talking about that, but we can't model that in an animal from an efficacy perspective, so, what is too much of an impact or at what point should we be concerned about it? Comparisons to available passive immunization products, both quantity and quality of responses, RIG, and research gaps that remain to be filled. And we have more time than I thought, we're going to run until 1:00, so I'm not rushing us. So, since I interrupted the ongoing discussion, talking about the vaccine inhibition, at what point does it become a concern? For example, if it's worse than approved RIGs, are we concerned or is there more leeway that might be considered?

DR. BLANTON: I -- so in -- my thought is that I would generally tend to agree with Dr. Fu,

that there certainly seems to be a lot of evidence that there is a statistical interference, but it's probably not (Inaudible) clinical impact from the studies (Inaudible), I'm sure others can add to that. So, I think that's probably the key question is, does the interference actually impact the serological level that we would be concerned or is that dropped back (Inaudible) 0.5, I mean, to some defined level.

DR. GUNALE: Yeah, I am Bhagwat Gunale from Serum Institute. So, I had a point to that vaccine without the (Inaudible) immune response to vaccine is interfered by the passive antibody. So, we had done rabies vaccine trials and the Category 2 patients received only vaccine and Category 3, vaccine plus RIG. So, the antibody type GMCs were slightly lower than those who received only vaccine, but it did not impact to a significant extent that it was impacting the vaccine. So, slightly lower, but it is not very dramatically low.

DR. DEMING: Now, is it possible that

these reductions might be more significant in those rare cases where we have a very late presentation of disease following infection? So, for when you get, you know, outwards of a year that you start to develop symptoms from (0:41:06.0) exposure. I mean, do you think that in that case any reduction or even modest reductions might be more of a concern?

DR. GUNALE: I'm sorry, I was talking this from the human perspective. Are you asking from ...

DR. DEMING: Yes. So, we're -- the general consensus that I'm getting so far is that reductions in vaccine response are expected with the passive immunoglobulin. If with a new product, it's -- that impact is more pronounced than what we see with approved RIG, even if in most cases, it has no clinical significance, in those rare cases where there is a very late presentation of disease, do you think, in those situations, it might be more meaningful?

DR. WILDE: Well, this has been

discussed, you know, (Inaudible) by people like us and I think you too. You have a patient coming in late, you know, and there is a question, it's day eight or day nine, and it's a very, very severe wound and the patient had one shot of rabies. See, these are the things that we are troubled by in a hospital setting with patients. And sometimes there is really no good answer to it, you just have to use common sense, and probably, we have discussed this several times and I think you probably have too. You know, someone comes in, he's had one or two shots of vaccine and he's got horrible wounds, multiple, multiple wounds from a proven rabid dog. And you can stand around, three or four experienced people have seen this before, with completely different opinions and there's no good answer to it. And I've never done it, but that almost, you know, informs my grey hair, my seniority, to say no, we're going to double the dose, because it's now or never. Because one thing we all believe in, that it is the first few days when you interfere that makes

the difference between life and death, And you all, you know, know that too. That's nothing new, it's no rocket science. So, you have to do the best you can and the only other problem, is even in Thailand, you incur a medical-legal issue, because people read, they listen to TV, they know a lot, and they are coming back with a couple lawyers if you do something strange. And that swayed me once or twice when I got -- particularly phoned, you know, because you get phone calls. Don't you get phone calls? They don't know your number. Well, you're lucky. But you see, there are very difficult questions like this. We don't really know what happens with the wound side, what happens with the nerve side.

DR. BROWN: So, this is Catherine Brown with the Massachusetts Department of Public Health and I just -- I wanted to build on that, which is, I think your question is almost impossible to answer since we don't really understand the factors that affect that incubation period. Particularly, for those really, sort of, you know,

way outside the Bell curve incubation periods. So, nobody knows yet.

DR. WILDE: It's a gap (Inaudible).

DR. FEHLNER-GARDINER: I think -- I'm not a clinician, but in the -- in -- maybe some of the panel members can comment, but in the cases of these very long incubation period human cases, for the most part, those people did not receive post-exposure treatment at the time, and so the question of whether a slightly lower response had they received PEP, again, I don't think you can answer that, because had they received the PEP, they probably wouldn't have developed rabies. So, those long incubation ones are where the people were never treated appropriately.

DR. DEMING: That's interesting, thank you.

DR. FRANKA: (Inaudible) going, but Susan was first.

DR. MOORE: Thank you, Richard. I just wanted to mention that if you look at all the challenge studies, and there's a lot out there, what is very consistent -- and we're just

publishing a paper on this and that's why I'm speaking on it. There -- no matter what the serology was, if it's above a certain level, there's a good chance of survival. So, if there's some reduction of antibody response due to the interference, as long as it's above, you know, say one at a certain time, then there's protection. And also the challenge studies, you have to remember are, there are severe challenges. Many of them are injections, right, into the brain. Some of them are, you know, not as severe, but all of them I looked at, as long as the subject developed antibody within, you know, the normal, what, 14 to 30 days, no matter how long it was until the challenge, you know, to -- the probability of survival was good if they developed a robust response, because they developed memory cells. And they may not have an antibody level at the day of challenge, but that -- the memory cells are there to get that immediate -- and that's what we all know, is that you have to have a fast rise in circulating antibody to survive.

DR. WILDE: The only place where you may make an interference in the course, in the clinical decision, is when you have a patient coming in and they have peripheral circulation antibodies. And if on top of that, you find antibodies in the spinal fluid, this is a patient that should be in a teaching hospital with all the plugs taken out of the system, and this is a rule that we actually have in the tight guidelines, we've got that in there, but we've never implemented. And I've never seen a patient that came in like that, like the Wisconsin one. The Indian ones had a couple, I think, published a couple cases that came in with circulating antibodies, and I think one, if I remember right, had spinal fluid detectable antibodies and he still died. But these are the patients that need to, you know, have an effort made if you have the means. Otherwise, just, you know, comfort, care is what's in order. So, you're -- you know, it's very important for people to send, you know, an answer to you and you have to give an early answer

to be effective. You know, that's -- and it's -- the likelihood of that money having been spent appropriately and effectively are very, very small. We have never seen a spinal fluid come in, you know, in a, you know, retrievable state. You know, you see it if you keep people -- you know, a person artificially alive for a long time and you can do that today, you know. My -- where I trained at the University of Alberta in Edmonton, they had one -- what was it? Several months. They had a vegetable and they described the -- in the internal report, they described the brain, when they opened it, it looked like toothpaste. So -- yeah, there's a lot out there that we can still write papers on and get promoted, but whether it's worthwhile is another question. But I think what you guys are going to do with the serum is definitely worthwhile, and I take back an (Inaudible) report that I made. You know, don't interpret then that I'm trying to discourage you, but I think it's a tough issue. It's necessary and I hope you persevere.

DR. CONNELLY: So, I just wanted to explore just one of things that was being talked about and just pose a hypothetical. So, we had talked about, before that, when you're selecting, potentially in animal models, the monoclonal antibody dose to move forth with, we're talking about having enough in that early window period. But then there's also been talked about, even when there was the development of the original HRIG products, not to pick a dose that doesn't significantly interfere how you define that with the active immune response. So, my question is, as a monoclonal antibody dose is being selected, looking at those two factors, as it moves forward, how -- if you have a scenario when you're comparing it to the rabies immunoglobulin, plus vaccine product, just if you see a difference in the rabies virus neutralizing antibody, just how do you put that into context. So, is it just a threshold that it needs to be above, is there a degree beyond which it's -- the difference is too much, because we've already talked about that even

for HRIG, initially, a dose was picked -- the higher dose wasn't selected to move forward because of that later response, so, just trying to think about interpretability of monoclonal antibody dosing in comparison with available passive immunization products in that later phase and just trying to get a better understanding of what that later data can or cannot tell us.

DR. FLEMING: Fleming, I've been waiting to kind of jump in because there surely are very significant benefits and insights that we get from the animal studies and the serologic evidence and the clues that we get. But you're raising a really good question. This is so multi-dimensional in terms of what is the magnitude and duration of effect that you need to have to -- that is sufficient to achieve what we clinically care about which is to protect the patients to reduce mortality. And so we talk about what are the use of the serologic assays in the animal studies and there's -- they're absolutely highly useful proof of concept, they're absolutely highly

useful as you're trying to guide how you're managing patients in a given clinical setting. The question is, do they truly tell us the essence of what we need to know for causality? Do they tell us the essence of what we need to know -- we're going to discuss this this afternoon which is, can you base an approval decision on looking at effects on these --

DR. WILDE: (Inaudible)

DR. FLEMING: -- serologic assays and neutralizing antibody levels? So, we heard from Dr. Moore, very important insights this morning that in animal studies, the rabies neutralizing antibodies are really a strong correlate with mortality, okay? Be careful, though. That is not a correlative protection, that's a correlative risk. A correlative risk is not a surrogate of protection. So, it doesn't mean that specifically causally inducing an 0.5 international unit protects you. And is it day 14, is it -- as we were just hearing from Sarah, is it -- what about the positive things that we're inducing if we get

a better response at day 2 to 7, but we somewhat attenuate the effect later on, how do you know? So, fundamentally, what I would want to know if I'm using these as the base -- if I'm going to use neutralizing antibody responses as the basis to judge whether or not I should use an intervention or whether I can replace HRIG by monoclonal antibody is I need to be able to understand the timing, the magnitude duration, and the breadth of the effect by an intervention on this measure that is required for protection of mortality.

DR. WILDE: Well ---

DR. FLEMING: That is is a far more complex issue than understanding whether it's a correlative risk. It's understanding whether it's a surrogate of protection. And my fear is we heard two examples this morning where we had Phase 3 studies that were designed based on using as the Phase 3 end point the RFFIT titer greater than .5 at day 14. Why .5 versus .4, .3, .7, why day 7 versus day 10 versus day 14, why not other aspects to all of this? So, I suspect part of the causal

mechanism is mediated through the neutralizing antibodies. But at what magnitude, at what duration, at what breadth? And these are issues that technically are only understood when you have an array of clinical trials that show that the effect on the biomarker predicts the effect on the clinical end point, not that it's a correlate. We haven't seen any of those kinds of data.

DR. WILDE: Well, you know, I would like to -- really, I don't understand how this would change my decision making for the patient. They -- you know, how to manage that patient, whether the antibody titer is 0.7 or 14, I would do exactly the same thing in a clinical way. Now, maybe you can figure something out for -- you know, for you, your business, in thousands of patients by now, probably, where you can get an overall pattern. But I've seen people survive, you know, with very, very low antibody titers, less than 0.5. And furthermore, you have something else in humans, which you probably also have in animals, and that is low survival -- low

antibody responders. When you do a clinical trial, which we've done many years ago, I don't do that anymore, it's kind of boring, and you work for the pharmaceutical industry when you do it, and you have to write that every time you publish a paper as a bias for five years. So, you know, it's -- there are low responders and in every large study that you do when you have a serial study, you find people all of a sudden have extremely low titers or very high titers. And you catch the patient and sit down with them and say, 'You know, did you ever get bitten by a dog'? And he says, 'Well, I have to ask my grandmother and she told me' -- you know, he calls you back, 'yes, I had Sample vaccine'. Another comment I'd like to make is, you know, I was listening a lot and keeping my mouth shut, trying to figure out what's really going on. The Sample vaccine used to be a very potent inductive, all kinds of cytokines, and some of the cytokines are potent killers of virus. And so, there was another factor when you're quoting all these great results of Chuck -- well,

not Chuck, he came after that. But yeah, -- well, the real old timers, those Indians or whatever in the olden days, the Frenchmen, they used Sample vaccine and they had completely different results. They responded very, very highly with antibodies. We had one guy, my former boss, the dean at (Inaudible) Infectious Disease (Inaudible). He did a huge study in Khorat (ph), which is a large city with reasonably good -- even at that time, good facilities, and he used only Sample vaccine. He published this in a first class journal, you can look it up. And he had no death. There were hundreds of people and they had -- you know, they didn't know if all the dogs, of course, had -- really had rabies or if they had rabies in their saliva. But statistically, it was something where -- there surely were a lot. They had survivors and people attacked them.

DR. DEMING: Forgive me for just a moment, but we're in the last ten minutes, so I'd like to open it up to the audience as well to ask questions, but Dr. Nelson?

DR. NELSON: Yeah, I'd just like to follow up with a comment, but sort of a question that follows a bit on what Tom Fleming mentioned. So, I was sitting here thinking that the selection of this .5 international units per millimetre may be related more to vaccine response than it might be related to immunoglobulin response and this day 14 pick, because it seems to correlate with vaccine response. And so the hamster model doesn't address that, which is why I asked about the use of the immunoglobulin alone. And the other concern, I was doing some math, I mean, you have -- in the Phase 2, 3, you have 100 people who have a Category 3 bite. And I don't know the data in India, but if I take the dog data from the Philippines, that means only 25 percent of the dogs actually were rabid, of which only, if I take the data from those that are actually shedding, of which only 15 to 18 actually were shedding rabies at the time, and so you have a zero out of 15 or 18. And I can't do confidence intervals in my head, but I'm sure Tom could, that zero out of 15

or 18 is probably a confidence -- it'll round up to maybe 20 percent failure. Is that close? Close. Yeah, so basically, all you've ruled out is a 20 percent possibility that in that Phase 2, 3 trial, you could still have 20 people die. And so, it just raises questions, to me, about the usefulness of the serology, if, in fact, what's happening is you're trying to prevent the vaccine at the wound, because it sounds like once it's in the nerves, you're done for. Is that correct?

DR. DEMING: Yeah, it's correct.

DR. NELSON: So, I guess it's not clear to me how that serological data allows you to move forward, other than saying if we get into the wound, right, we'll be okay. So, I -- it's kind of what I picked up listening.

DR. FEHLNER-GARDINER: I could comment. I think what's important about the serology in that initial phase before there's an act of immune response, and the comparison that needs to be made with the accepted product, which is HRIG, is the half-life. How long does that antibody stick

around before it wanes and you're expecting the active immune response to take over? And so I think the Phase 1 trials that you've done have shown that the half-life at the different doses -- and that maybe speaks a little bit to the question of what dose should be used, is that if we assume that HRIG and ERIG, which have been used for a very long time, if the half lives of those active ingredients are considered effective, then for the monoclonals, we don't want to see anything less than that. We want to see a neutralizing antibody titer that lasts for an appropriate length of time and something that is comparable to the immunoglobulin products. That's kind of my take on it.

DR. WILDE: The importance of that is much less than we thought before, because we know now that's what's happening right away, and it saves your life. And you know, I got shown wrong not being up-to-date when I was told, you know, the immunoglobulin that you give the exposed animal, that the animal will survive, because the

-- you know, the thinking before was that the duration matters. And we know now it probably does matter sometimes, but not like we used to think.

DR. SIBERRY: Can I press Dr. Fleming a little bit on this? Because I feel like we were headed towards the idea of efficacy being something as measured by some serologic correlate that people had accepted. I'm hearing you sort of press us to say that in your mind to think about product efficacy for this, you think we need to have a clinical end point that gets measured. I just want to make sure I'm understanding that right and -- because that would have big implications.

DR. FLEMING: At the end of the day, what we're talking about are interventions to provide clinical benefit to patients. And this is a setting of huge need, this is a setting where we need interventions to prevent mortality. And we have extremely effective strategies in hand, but there are issues with the combination of the

vaccine, and HRIG as I understand, in terms of supply and toxicities, et cetera, where some -- in some settings, it's not readily available. So, my sense of where we're going this afternoon is in those settings, what can we do, and should monoclonal antibodies be studied as an alternative to HRIG, particularly when it's maybe not as readily available, that would be efficacious? Efficacious mortality, efficacious feels -- function survives. What has the patient experienced? How do I think I'm going to get there, I'm going to get there probably by inducing an immune response, by inducing what we're, at best, probably assessing today, serologic measurements, neutralizing antibody, etcetera. But how do I know what is the true causal level, what is the level of effect in terms of the timing, is it enough with the vaccine? Well, maybe not, because the vaccine effect kicks in at Day 7. Does the -- does -- would the monoclonal antibody or HRIG improve mortality by kicking in on Day 2 to 7? What are the data that show that

and, in fact, do we even know what HRIG does to mortality? Much less, do we know that it's mediated through the effect on what we would represent as neutralizing antibodies from Day 2 to 7, how much effect is it? We have to know all of those things if we want to envision doing a clinical trial with a monoclonal antibody using a serologic end point, so that at the end of the day, (Inaudible) non-inferiority trial. So, if you're saying I'm going to lose a certain amount of neutralizing antibody effect, I have to know what is the amount that I can lose that translates to an acceptable loss of effect on mortality? And I've not seen any data yet that tells me causally --

DR. FU: Yeah, yeah, (Inaudible)

DR. FLEMING: -- what's the effect on serologic measures that translates to an effect on survival. And that's not obtained by correlates of risk, that's obtained by surrogates of protection. And we have -- if we had ten hours, we could give ten hours of examples where

correlates of risk don't translate to surrogates of protection. At the end of the day, I need a surrogate of protection if I'm going to use this measure, if I'm going to use a serologic measure for a Phase 3 trial, I'm totally for using it for proof of concept, guiding clinical care in the absence of other data. But eventually today, we're going to be talking about what would be a definitive endpoint and I'm worried that I saw two examples this morning where it looked like we were using RFFIT titer greater than .5 at Day 14, and I have no basis to understand whether causal effects on that translate to causal effects on mortality.

DR. FU: Day 14 is for vaccine, not for antibodies. Antibodies, (Inaudible) say Day 1. But rabies (Inaudible) for long time, the virus neutralize the antibody possibly is the best correlates for neutralizing the virus to protection. It's been done a lot, we know (Inaudible) contribute to protection, (Inaudible) cytokines, everything. But ultimately is the neutralizing antibodies, all right? If you know

it -- if you have the neutralized antibody, you can protect. We're talking about the hamster model, Dr. Wilde was thinking otherwise, we have done a lot of studies. If you have a neutralized antibody, (Inaudible) going to be protected. (Inaudible) virus you can use.

DR. DEMING: That's a correlative risk. That's a -- it's useful ---

DR. FU: Yeah, but ---

DR. DEMING: It's a correlative risk (Inaudible) surrogate of protection.

DR. FU: I'm not sure they (Inaudible). But I'm not -- what I know from my own experience, if you have neutralized antibodies, you're going to protect. Humans are the same, animals are the same, so I don't think it is -- I'm not sure for the FDA to approve products what exactly we know, because, you know, rabies is very different. You cannot do a clinical trial with real rabies cases. Even with the exposure, you know, when this is a Category 3, the animals bitten (Inaudible) rabies. Even in that situation, you cannot have a control

group. You have one group, (Inaudible) in a group. From the previous experience with HRIG, with the vaccines, it protects very, very well. That's -- it doesn't matter -- I run studies, we're talking about, you know (Inaudible) from all the experience, because antibody plus vaccine works. So, I think here, if you want to approve the monoclonal antibodies in replacing or in conjunction -- whatever you think about with HRIG or ERIG is actually, if you have the -- enough data to support the mAb, it can neutralize different viruses in the level it's compatible to the HRIG or ERIG. That would be my thinking from that point and if ---

DR. WILDE: Well, all the studies that we've done and my group has done, I don't even know how many, maybe five or six, (Inaudible) BCC (ph) from Japan. All of those were done with us and others (Inaudible) the only ones and they were all done on the basis that you do the study like it was discussed, and if the patient has any antibody titer detectable one year later, this

means 0.0 or something, detectable and response -- usually that's not done, but you can go that far, response to booster injection with an (Inaudible) response. If you have a detectable anti-titer and is alive, because it will also eventually have to be done with a group of people, which a significant number have been bitten by truly infected, this is the way all the studies were done. And your product, it's no different than HRIG or whatever. You just repeat that, don't complicate it. I mean, don't make it -- give people openers to start these kind of discussions that are absolutely not appropriate in my view.

DR. DEMING: All right. This discussion will certainly carry over into -- later into the afternoon. But we're done now, thank you all very much for the lively informative debate. It's very, very pleasant. And when do we meet?

DR. FEHLNER-GARDINER: Two o'clock.

DR. DEMING: Two o'clock, we'll meet back here again to start the next session. Thank you all very much.

(Off the record discussion)

DR. CONNELLY: Welcome back, everybody. I hope everybody was able to get some food. This afternoon, we will be focusing on clinical trial considerations and we will have two talks, one by my colleague, Dr. Tanvir Bell, who's a medical officer in the Division of Antiviral Products at FDA, and by my statistical colleague, Dr. Thamban Valappil. And then this will be followed by Dr. Holly Taylor's ethical considerations talk. So, with that, I will turn it over to Dr. Bell to get us started. Thank you.

DR. BELL: Can you hear me okay? Good, thank you, Dr. Connelly. In my talk, I plan to bring elements of talks and discussion from today and express some concepts about clinical trials with a novel rabies monoclonal antibody product. I hope to set this stage for a productive afternoon panel discussion, and based on what I've heard this morning, I don't think that should be a problem, focusing on challenges in clinical trials with a novel rabies monoclonal antibody product.

I'll first remind you -- oops, sorry, I didn't advance the slide. There we go. This is an outline of my talk. I'll first remind you about the current PEP landscape, then I will discuss the role of serologic assays in rabies product evaluation. Next, I will discuss aspects of clinical trials in healthy volunteers. This is akin to earlier phase studies, your traditional Phase 1, Phase 2 studies. I'll follow that by trials in suspected rabies virus exposed population. During this part, I'll turn my talk over to Dr. Valappil, Statistical Team Leader, who will discuss superiority and non-inferiority trials. Safety in an infectious disease agent such as rabies virus with a high mortality is of paramount importance and may be tied to demonstrating product efficacy. I will discuss some concepts about safety of a novel rabies monoclonal antibody product. I will conclude by discussing potential knowledge gaps. You've seen a slide earlier today and I show it again to you as a reminder of the current recommended PEP

regimens for high risk animal exposures. The CDC, ACIP on top, and the WHO recommended PEP for the circumstances listed on the slide, the CDC by animal type, and the WHO by exposure, Category 2 and Category 3 of different elements. It's important to realize that PEP should begin as soon as possible, though there are no time limitations beyond which use of PEP is not recommended. The elements of these two regimens consist of extensive wound cleansing, rabies immunoglobulin, and rabies vaccine. It's important to highlight the different specific PEP regimens in different parts of the world are present. Such as equine rabies immunoglobulin, and we discussed this a little bit this morning, and also intradermal vaccine. This impacts -- this may impact the design of international trials and the interpretability of clinical trial results. These two prescribed regimens are considered highly effective. However, there have been reports of occasional failures, despite apparent adequate PEP administration, and this morning, we learned from

Dr. Wilde, some of his stories of success. But there still are problems that occur, leading in patients having rabies. Some most commonly hypothesized explanations include, the RIG may not be used at all, injected only IM and not into the wounds, or not all bite wounds are injected. Perhaps the vaccine or rabies of low potency. An exceptionally large rabies viral load was introduced by the animal bite. Any typical virus that is not neutralized by RIG or by natural antibodies resulting from vaccination can be the culprit. Lastly, inadequate wound care may be the issue. We do not -- lastly -- and also we do not know how often RIG is given without -- RIG is not given, this may be fairly frequent. In thinking about clinical trials and a novel rabies products, I want to revisit the slide. The solid blue line is where vaccine induced tumoral response takes place beginning about day seven to ten and then increasing. This also illustrates the window period when protection by giving RIG is shown, and this is shown in the highlighted yellow line. The

RIG should provide some activity at neutralizing rabies virus. RIG may be injected at the bite side and/or symmetrically. Serologic assays can assist in possibly interpreting antivirus activities and are available. This morning, we learned about series virus neutralizing antibodies -- I'll refer them -- to them as RVNAs -- from Dr. Moore. This slide is to remind you about the ACIP and WHO guideline recommended minimal acceptable RVNA levels of 0.1 IUs per ML, and 0.5 IUs per ML respectively. And this too was discussed in the morning. We need to recognize, as was mentioned in the morning panel, that RVNAs have been applied clinically to evaluate vaccine effect, and that there is no established RVNA threshold for a passive immunization. Further, other aspects of vaccine response may influence RVNA levels seen after vaccination. For example, cell mediated immunity and capacity for an anamnestic response. Here, I present a hypothetical example of dynamics of RVNA levels in the context of a passive antibody product with or without rabies vaccine.

The graph has on the Y axis, rabies virus neutralizing titer, and on the X axis, time. There are two key points that we need to consider with the use of an antibody-based component of PEP in combination with vaccine. And this applies whether the antibody is (Inaudible) from serum, or it's a monoclonal antibody, or an antibody cocktail. Now, I'm going to walk you through the slide. In red is the hypothetical antibody alone -- I'm sorry, in red is the antibody alone, and in blue is the virus, the effect of the virus alone. Now, there are two more lines, which represent the antibody at higher levels, with -- and the antibody at a lower level. Both of these are given with vaccine. The first key point, can the antibody be present in sufficient levels to (Inaudible) protection, during the window period, prior to development of an immune response to the vaccine. As shown in this area, all three antibody products have higher levels of RVNA compared to vaccine alone. The second key point, does the antibody impair the immune response to

the vaccine. Both the antibodies with vaccine impair the immune response, however, the higher dose vaccine in green -- the higher dose antibody, I'm sorry, with vaccine, impairs the immune response from the vaccine more so than the lower dose antibody with vaccine. The goal is to achieve enough RVNA activity in the window period, without compromising the vaccine effect. This slide presents possible challenges with interpretation of serologic assay data as it pertains to these questions. What level is needed during the first few days of protection, and what time points should serologic assays being measured? Can assay results for MAbs and HRIG be compared and what level of comparability is sufficient? What do serum measurements tell you about protection of the wound site? Is there any other way this has protection at wound site in the clinical setting? You've seen this slide earlier today, presented by my colleague, Dr. Connelly, and it is relevant to reiterate important context when moving to clinical trials and human healthy

volunteers. This is a time when it is of utmost importance that exploration of safety and (Inaudible) are characterized in a defined cohort of human subjects. In characterization of dose selection, these questions need to be considered. Can higher doses be identified as excessively interfering with active response to vaccine? Can lower doses be identified as unlikely to provide adequate protection in the window period? In addition, we pose a question to the panel. What serologic assay parameters, level and timing, are most predictive of protection after rabies exposure? These next two slides illustrate important questions to ask regarding interpretation of RVNA data. When comparing a hypothetical monoclonal antibody and HRIG, both with vaccine. We must ask the question, when evaluating RVNA levels, how early or how late should RVNA levels be checked? In addition, how close in approximation should be the curves be? In this first hypothetical example, the graph depicts results evaluating RVNA and healthy

volunteers exposed to HRIG plus vaccine in red, and monoclonal antibody plus vaccine in green. The rabies vaccine alone is in blue. The Y axis is in logarithmic scale on the slide, and in this graph, and the X axis is time again in days. In this first -- sorry, the result shows that in the window period, the RVNA levels, between HRIG and the monoclonal antibody, both with vaccine, are similar. However, in the late period, the levels are different. The vaccine response is compromised more in the antibody arm, green, over the HRIG plus vaccine arm, red. In this next scenario, the result shows that the window period, day zero, day one through day seven, the monoclonal antibody response is significantly lower than the HRIG response. However, in the late period, the vaccine responses seem similar. These two examples illustrate the challenges and interpretation of RVNA in data comparing monoclonal antibody with vaccine to HRIG plus vaccine. And we welcome discussion from the panel. These hypothetical examples do not account

for administration of passive antibody into the wound site, as recommended by guidelines. Raising the question, how much do serologic measurements after IM injection tell us about neutralizing activity at the local infiltration at the bite site? But on the other hand, is there a better way of measuring what is happening at the bite site in the clinical setting? Then there's the other issue of complex wounds, multiple wounds, or occasions where no wound is visible, such as in a bad exposure. I want to reinforce that in proceeding with the trials in rabies exposed population, that it is of paramount importance that the totality of the available animal data, cell culture data, and clinical trials in healthy volunteers, support proceeding with trials in rabies exposed individuals. We must avoid unnecessary risk in the setting of a potentially fatal disease. This is both an ethical and safety issue. Additionally, the choice of dose is critical for beginning trials in rabies exposed patients, because the outcome of PEP failure is

dead. Clinical trials to show whether a product actually delivers the benefit that it is proposed to deliver are important from a regulatory perspective, but also for (Inaudible) public health and clinical decision making. This aspect and data aligns with the FDA's mission statement. We recognized there are many challenges in designing and interpreting clinical trials of a potential novel component for rabies PEP. In trials, in a rabies exposed population, I want to point out the clinical importance of having an active control comparison, monoclonal antibody plus rabies vaccine, to rabies immunoglobulin plus vaccine. This is because RIG plus vaccine is a highly effective approved regimen and the outcome of PEP failure is mortality. Now, I turn the talk over to my colleague, Dr. Valappil, who will discuss clinical trial designs.

DR. VALAPPIL: Good afternoon. I will now discuss some of the trial design considerations for the purpose of generating discussion among the panel. Generally, clinical

trials are designed to demonstrate superiority or non-inferiority. The objective of a superiority trial is to demonstrate that the new product is superior to the control, while the objective of a non-inferiority trial is to demonstrate that the new product is not unacceptably worse than the control, based on pre-specified non-inferiority margin. When considering any possible clinical trial design in the suspected rabies exposed population, the goal of the trial should be to assess the decrease in fatal rabies infection. In the next few slides, I will present few hypothetical trial design examples, using survival or mortality as outcomes, although other endpoint can also be considered if they are clinically meaningful. Now, we'll start with the hypothetical active control superiority trial using survival. As you can see in this example, subjects are randomized to receive either a novel monoclonal antibody or HRIG, in addition to vaccine. The benefit of such a trial design is that it provides direct evidence of treatment

benefit, and it's also easily interpretable. In terms of challenges, the success rate for the vaccine plus HRIG group could be very high, which would make the ability to demonstrate superiority probably difficult. In addition, there could be sample size implications, depending upon the treatment difference among the groups. In the second hypothetical design, you will see that it differs from the first example, as it includes a third arm, and subjects are randomized to receive either monoclonal antibody, HRIG or placebo. This trial is beneficial as the comparison between the test and placebo control arms provides direct evidence of treatment benefit, and the inclusion of HRIG control arm will allow for any assessment of the internal consistency of the treatment effect. In terms of challenges, it may be difficult to demonstrate superiority depending on the population enrolled, and the potential for high efficacy of the vaccine alone arm. Ethical concerns are also important. An aspect to designing a superiority trial is the consideration

and calculation of the sample size and this may impact the feasibility of the trial design. As shown in the table, the first and second columns are the individual rates for the control and test groups, respectively. The third column, is the treatment difference in this hypothetical scenario. As the treatment difference increases, as you can see in the third column, the required sample size decreases. For example, if you look at the third row, for the treatment difference of three percent, you can see the sample size has reduced to 450 patients per arm. Having discussed superiority trials, let us see an alternative option, which is non-inferiority. I will initially orient you to non-inferiority trials and its considerations. I will be followed by Dr. Bell, who will continue with the aspects specific to rabies virus exposure and related issues. As previously stated, the objective of the non-inferiority trial is to demonstrate that the efficacy of the test product is not unacceptably worse than the control based on pre-specified non-

inferiority margin. The non-inferiority trial is dependent on knowing the treated effect of the control, generally based on external information. In the diagram, the red dotted line indicates the non-inferiority margin. The point estimate of the treatment difference, and its corresponding 95 percent conference interval, between the test and the active control groups, are also displayed. As you can see, the lower limit of the 95 percent conference interval for the difference is above the non-inferiority margin denoted by the red dotted line. Therefore, in this hypothetical scenario, we would conclude that the test group is non-inferior to the active control. A few of the key concepts of non-inferiority trials include assess sensitivity, constancy and quality of the non-inferiority trial. Assess sensitivity is the ability of the non-inferiority trial to distinguish an effective treatment from an ineffective treatment or a product, and on reliably knowing the expected effect of the active control. The expected of the active control

relies on information external to the non-inferiority trial, based on the historical evidence of treatment effect. The constancy assumption requires that the information used to establish the effect of the active control treatment is similar to that of the current non-inferiority trial. For example, past studies establishing the effect of the active control should have a similar patient population, outcome of interest, and dose that of the current non-inferiority trial. Comparing these two types of designs, it is important to understand that any kind of sloppiness can lead to study failure in a superiority trial. However, in contrast, poor quality and conduct can potentially be rewarded, leading to falsely concluding non-inferiority trials. Therefore, the quality and conduct of the non-inferiority trial is critical. For a non-inferiority trial, there are two types of margins, margin considerations, M1 and M2. M1 is the entire active control effect over placebo, based on historical evidence of treatment effect. When

there is known heterogeneity of the active control effect, related to patient or disease characteristics, it may be necessary to adjust the estimate of the effect of active control, which is also called discounting of effect size. M2 is the clinically acceptable loss of efficacy for the test product compared to the active control. M2 should be less than M1, as we don't want to lose the entire effect of the active control, in support of the new product. This hypothetical schematic illustrates the non-inferiority margin determination as an example for you. The X axis shows the treatment difference between the active control and placebo. The point estimate, and the 95 percent confidence interval to the right of zero, illustrate the historical treatment effect of the active control product. Based on the lower bound of the 95 percent conference interval, we can say that the treatment effect of the active control relative to placebo is four percent. This represents M1. Based on a clinical judgement, if you are willing to accept a two percent loss in

efficacy, while preserving two percent of the control effect, we can say that it justifies the two percent non-inferiority margin, say M2. To conclude, I will discuss the benefits and challenges for the non-inferiority trial in general. A benefit of a non-inferiority trial is that the design provides a potential pathway, to assess effectiveness if a superiority trial is infeasible. However, the choice and justification of the non-inferiority margin, and the potential implications on the sample size, are significant challenges in many NI trials. I've only spoken in terms of general non-inferiority aspects, but there are specific challenges that will arise in clinical trials in the suspected rabies exposed population. For example, the interpretation of the findings may be challenging, if the contribution of HRIG added to vaccine is unknown or unreliable for the mortality endpoint. Reliability of the contribution of HRIG should consider the similarity of the historical population, including the vector, bite sites,

differences in strains, and also the management. Maybe there are other issues as well. I will now turn the podium back over to Dr. Bell to continue with the remaining portion of the presentation. Thank you.

DR. BELL: Back to my height. Can you all hear me okay? Good. Yes? Okay, good. Thank you Dr. Valappil. I will remind you and give a little detail about the Iranian wolf serum -- wolf experience. The Iranian wolf experience, with rapid anti-serum, reported in the 1950s, is the foundational study establishing the role and contribution of passive antibody. The lone wolf attack led to 18 severe head wounds and 11 limb or trunk wounds. The contribution of anti-serum is seen amongst those subjects who had severe head wounds. A total of 13 peoples received rabbit anti-serum and sheep brain derived vaccine. Seven subjects got a single injection of serum with rabies vaccine, and there was one death. Six subjects received two or more injections of serum with vaccine and there were no deaths. Among

those with head wounds, who received only vaccine, there were three out of five deaths. Of the 11 trunk -- limb or trunk wounds, there were no deaths amongst those receiving vaccine with or without anti-serum. There was a decreased mortality from 60 percent to eight percent in those with head wound bites when serum was added to vaccine. These, again, are the foundational data that established the protective role of passive antibody in rabies PEP regimen. Although these data suggest a substantial contribution of anti-serum in this particular situation, there are limitations in generalizing the treatment differences observed in this trial. These include a small sample size with only 18 people with head wounds receiving an intervention. This wolf attack was an unusually severe attack scenario. In this trial, they used a different vaccine, a sheep brain derived vaccine, than those vaccines currently used today. A different passive antibody rabid anti-serum was used, and the route of administration of the (Inaudible) serum -- of

the anti-serum was IM and not into the wound. As Dr. Valappil pointed out, in establishing a non I -- NI margin assumes consistency of the treatment effect, which is not apparent from these data. We've talked about superiority and non-inferiority trial designs. Are there other trail design considerations in suspected rabies exposed population that may be feasible, ethical, and interpretable? This may include a dose response trial, although it is subject to at least the same issues as a superiority trial. Or it may be a historical trial, but this is subject to at least the same issues as a non-inferiority trial. We invite any other ideas for discussion among the panel. Prior clinical trial examples in this talk have used mortality as an end point. This slide discusses potential use of alternative end points. I want to point out that alternative end points are useful if they are predictors of mortality, and Dr. Fleming brought up this concept earlier in the morning panel discussion. Assuming challenges previously discussed regarding serologic assay

interpretation in the healthy volunteer population are clarified, to inform functional contribution of passive antibody in the window period. We ask the questions, in what ways can serologic assays be informative in trials in suspected rabies exposed population? What time points are informative? In measuring men -- different times -- if measurement times differ from healthy volunteer studies, why? We ask the panel, are there other measurements that maybe information? In addition, what duration of follow-up is needed to establish clinical relevance? There are geographical differences in rabies animal vectors, virus strains, and PEP regimens. This leads to consideration about interpretability and generalizability across different populations at risk. Trial psych capability's important, confirmation of rabies status of the animal, serologic testing, and patient follow-up should be optimized. We learned this morning that Dr. Quiamboa's site is able to have resources to do some of these functions. Possible inclusion

criteria considerations may be, enrolling low risk WHO Category 3 exposures initially, such as those patients or subjects with limb wounds, followed by higher risk exposures. If this strategy is used, can results be informative in a low risk population who may be expected to have high survival with adequate wound care and rabies vaccine alone. Another consideration would be enrichment with population experiencing more severe head wounds, and the third consideration is timing of enrolment after the clinic -- after the animal bite. These are just some additional considerations for clinical trials in a suspected rabies exposed population. Assuring and advising about safety of a novel product is of utmost importance in drug development and approval. Now, this slide lists potential safety concerns with monoclonal antibodies. Experiences with monoclonal antibodies, in general, have shown side effect, such as allergic-type reactions, flu-like symptoms, gastrointestinal symptoms, and hypertension. The full safety spectrum of a novel

monoclonal antibody for rabies is yet to be defined. Similar reactions can occur with plasma derived products. And it is important to highlight that efficacy issues for rabies monoclonal antibody are also safety issues with the end result of disease, of death. This includes vaccine interference and a narrower spectrum of rabies virus coverage. I will conclude with potential knowledge gaps, and hope of these gaps can be discussed in the afternoon panel discussion. The contribution of passive antibody -- in the contribution of a passive antibody, HRIG, or monoclonal antibody, to rabies PEP regimen, may be difficult to ascertain. When does current PEP not work? Case reports of PEP failure do not provide information on what proportion of persons receiving current PEP, lacking only RIG components, develop rabies. Regarding clinical trials, what type of trials maybe -- clinical trial may be interpretable, feasible, and ethical? All these complicated issues surrounding rabies PEP in the context of a

new monoclonal antibody, should make for a good discussion. We'll learn more about ethical issue in Dr. Taylor's talk that follows. How can indirect measurements, such as serologic assays, apply to trials and suspected rabies exposed population? How can serologic assays help determine if people with rabies exposure are being protected from a fatal disease? We have serum measurements, but what about mopping up at the bite site, which may be the first line of attack against the rabies virus. What neutralization happens at the bite site and how can this be measured. I'm looking forward to these, and other discussion points, and I thank you, and it's been nice having people from far and near come to discuss this topic.

DR. CONNELLY: Great, that was a great overview. Now, we will have Dr. Holly Taylor provide a talk on ethical considerations in rabies monoclonal antibody development. We are delighted that Dr. Taylor is here with us, she is a core faculty member of the Johns Hopkins Berman

Institute of Bioethics, an associate professor in the Department of Health Policy & Management, Bloomberg School of Public Health. Dr. Taylor is trained as a social scientist and uses both qualitative and quantitative methods to explore topics in the ethics of human subject research and ethical considerations in public health approaches to infectious disease. So welcome, and looking forward to your talk. Thank you.

DR. TAYLOR: Thank you. So, I might need a lesson on moving forward, let's see -- yeah, okay. So, hi everyone. I'm glad you're all awake and perky for this afternoon discussion. So, I -- thank you for the introduction, and I will just add that I think a lot about public health ethics and research ethics, and this is a lovely example. In thinking about the fact that we have a variety of effective public health interventions to reduce rabies, and today, we're focusing on one those pieces, and I guess I want to remind us that there are -- there's a forest, and we're focusing on a tree. And when we're

doing ethical analysis, it's sometimes important to look at that forest as we then drill down to looking at the issues related to the tree in this case. And I mention that, because we're talking about comparing things to an intervention that we know is highly effective, and we have a number of other interventions that we know are highly effective. And one question might be how we think about investment in this one as compared to these others. So, I just wanted to put that in context. So -- sorry, moving forward, I have a number of slides that frankly just helped me orient myself into this space. And -- so, we have talked about a number of these issues related to the product of RIG, in terms of why we might be looking for alternatives, expense, supply, et cetera. And our goal is to find something that's safer, efficacious, and potentially more economical. In terms of considerations related to ethics, I was asked to focus on three particular questions, and I'm going to do that now. In terms of thinking about ethics, I've framed each of these questions

with the principle that I think is in play. So, when we talk about studies design, we often think about the principle of beneficence, that means that we're going to minimize risk and maximize benefit. When we talk about enrolling children in trials, we're often thinking about vulnerable populations and respect for persons, that's the ethical principle. And then, considerations around justice, how do we frame -- all of our discussion I think, though I'm not sure we've said this directly, we're not talking about conducting PEP trials in Silver Spring, we're talking about conducting them in rural developing low middle income countries, and it's important for us to think about what that means in terms of conducting these trials as it relates to concerns about exploitation. Whether it is actual or perceived, and considering those. So, I'm going to just walk through each one of these. So, we've talked also about what the standard of care is in this context and the different designs. I didn't know that my previous speaker was going to talk about these,

and spoke about them in a way that was very clear and certainly deeper knowledge than mine. But in thinking about these potential study designs, as we just learned, there are risks and benefits to all of them. I have the placebo trial on here really just as a straw horse, straw man, meaning that it would be highly -- I would -- I think, it would be highly unethical to launch a placebo control trial. And then there are cost and benefits to embarking on either a superiority or an equivalency trial -- or the non-inferiority, I guess is the other -- I think of it as equivalency, same a non-inferiority. So, when we're then talking about who would be enrolled in this hypothetical trail, the question becomes -- well, the fact is that 40 percent I think was quoted, 40 percent of the rabies or the bites are among children. How do we think about whether or not we would consider enrolling children in some of these hypothetical trials that were designing? And the concern, right? Is that when you have a child, the -- they are unable to provide what we

think of as appropriate informed consent. They are therefore vulnerable, we therefore go to their parents for permission to enroll them. We also, here in the United States, have restrictions on the type of research that can be conducted with children. When we talk then about conducting these trials outside of the United States, I'm not an expert on the types of regulations that exist in other countries, though I do know that in India, in particular, they have similar restrictions in terms of thinking about whether or not children are allowed to be enrolled in clinical trials. And in the United States, these are the circumstances under which it's allowed. That there is no more than minimal risk, more than minimal risk with the potential for direct benefit, or no more than minimal risk with the potential for benefit to the children with the disease or condition. I think it would be quite hard to justify inclusion of children in a -- in the first Phase 3 trials that we would conduct. I could probably construct an argument in favor of

it, but I would do so with some trepidation, given that I know that I can enroll fully competent -- well, hopefully fully competent adults into my trial first, and given the letter of the law in the case of requiring a potential for direct benefit, when we're talking about, perhaps randomizing individuals to something other than the current standard of care. And then lastly, I was asked to speak a little about issues related to conducting these sorts of trials in rural and developing areas. The primary thing we might be concerned with is a concern about exploitation, meaning that exploitation is when A exploits B, when A receives an unfair level of the benefits, and/or B receives an unfair burden of risks, as a result of interacting with A. And this most often comes up when you construct a hypothetical trial and someone says, 'You're just doing that trial in blank in order to bring that technology to us' -- meaning the United States or the western setting. Non-exploitation is when we make sure that the benefits of the research that you're conducting is

highly relevant to the population that you've enrolled, and you've anticipated in advance, ways to maximize the likelihood that those individuals will receive the benefit of the intervention you develop. So, there are certainly ways to avoid exploiting a population. There are certain circumstances where exploitation is more likely, and those are -- many of these have to do with feasibility and the ability of the host country and/or in terms of scientific or in health infrastructure. So, there may be less experience with research, less local infrastructure, less ability to give volunteer informed consent. And in part, what I mean by that, is that research may be either a foreign or unfamiliar concept, less experience with scientific or ethical review, and less infrastructure to conduct their own research. There are ways that we can minimize concerns about exploitation. As I sort of hypothetically mentioned, you think about where these studies being conducted, in what types of capacity building the investigators invest, and perhaps

more importantly, who will have access to the intervention if the research as a success, and who is responsible for that access. I've been thinking about the trials that were presented earlier today, and I don't know, but I'm going to hypothesized that the fact that the people who were the potential subjects came to a clinical setting with their injured family member, or brought themselves with their injury, and that they likely lived, either relatively close to that center or had transportation of their own, or some expectation that when they got on public transportation with their bite, they were going to get to the place they were going. So, in the studies that were conducted, and you guys can clarify for me, I'm assuming that they are not being conducted in remote rural areas where the likelihood of a rabies bite might be even more likely et cetera. So, just a number of things to think about. Another -- just other set of concerns or a way to think about of avoiding exploitation, are things like, you know there's a

greater prevalence in the setting that you're doing it -- conducting the trial. The question or the reason why you're doing it is more relevant there. There is some pre-existing relationship, which isn't necessarily determinative, but that sometimes enables the trial to move forward and is feasible and is likely successful. And then, we have to think about, sort of, issues around cost and expedience, and again that's not relevant either. I mean, it's relevant, but not decisive. In terms of thinking about ethical concerns, sometimes we -- when we think about ethical concerns, sometimes we immediately start thinking about either trial design concerns or feasibility concerns, and the reason we do that is because it's sometimes hard to pull those apart. And I'll just end again where I started in reminding us that this is just one arm, if that's the right term in reducing mortality related to rabies, and I'm not sure how that can be incorporated into our deliberation, but I think it's an important thing to keep in mind. Thank you.

DR. CONNELLY: Great, thank you. You may have noticed that we have -- we deviated somewhat from our original agenda. I want to point out that there had been time for formal public comments, however, we did not receive any formal public comments, which allowed us to move lunch and keep back on time. We will go ahead and take a 15 minute break. I think it's important for people to reflect on these two important conversations or presentations that we just had. Go ahead and get some coffee, and we look forward to the panel discussion that will follow in 15 minutes. Thank you.

(Off the record discussion at 02:48:38 p.m.)

(On the record discussion at 03:01:08 p.m.)

DR. CONNELLY: Okay, we'll go ahead and get started in the interest of keeping on time. Welcome back for the second panel discussion on clinical trial considerations. So, as we've heard, clinical development of rabies monoclonal antibody for use in post-exposure prophylaxis aims to demonstrate sufficient benefit for uses an

alternative to existing hyper immunoglobulin products. However, as you've heard, there are challenges in conducting clinical trials in this area. While non-rabies exposed healthy volunteers can provide some information about neutralizing activity in serum after antibody administration, the relation to protection against disease when used after rabies exposure, may not be straight forward. Because of the many factors contributing to non-development of rabies after post-exposure prophylaxis for suspected exposure, the absence of rabies may not indicate the effect of the passive antibody component. So, this panel section will focus on clinical trial designs, ethical considerations, and measurements that might aide in understanding whether a new rabies monoclonal antibody product provides early protection, prior to vaccine response, while not increasing vaccine interference. I should re-introduce myself, so I'm Sarah Connelly, I'm one of the medical officers here at FDA, in the Division of Antiviral Products. And I am very glad to be joined by my

co-moderator, Dr. George Siberry, and I'll let him introduce himself.

DR. SIBERRY: Certainly. Thank you, Sarah. George Siberry here, really nice to be here with you. I'm at the State Department at PEPFAR, the HIV Assistance Program by the US government, but I'm a Pediatric Infectious Disease Physician seconded from the Maternal Pediatric Infectious Disease Branch at NIH. So, pleasure to join this conversation. Sarah reminded me that fortunately our goal today is not that we all have to reach agreement or consensus on what we're discussing, but that this is really an opportunity for us as a group and individually to make sure that your input is heard on each of the issues that we have here. So, I'm going to ask everybody to be mindful of the amount of words they use to make their point, the amount of time they use, so that we make sure that we have the most opportunity to hear from the most people. And again, you don't have to convince other people, you just need to make the case for us to

understand your position, so that it goes into the mix that we all take away from here. So, Sarah has already outlined, and you can see in front of you the three categories of questions, ethical considerations in clinical trials, possible clinical trial designs, and then what we can learn from serum neutralizing assays in the context of these studies. So, why don't we kick it off with the first? So, I'd like to hear some thoughts about what people think are the most important ethical considerations. So we think about the role and how to test these monoclonal antibody products, in the face of having a comparison product that is thought to be efficacies, but not fully studied in the robust way that we might like, and with issues of availabilities. So, I'll open it up for some thoughts about ethical consideration to clinical trial designs. I'm going to look first right at Skip, because I think of him when I'm thinking about this.

DR. NELSON: Well, I'm going to answer that, but I'm going to do it, and -- by laying out

what I see as a three part program, and I'm going to put up as a potential target for other people to shoot at, as I've listened to this. So, it sounds to me one of the first issue is -- first of all, I mean in pediatrics, you don't want to expose kids to something that doesn't offer benefit or presents inappropriate risk, so part of the design of this is to figure out a way we can do that. And the second is, you don't want to withhold non-effective treatment from an adult that would result in serious morbidity and/or mortality, which is both the standard in the declaration of health safety, and the standard in ICH E10. So, we're stuck with figuring out how to go forward, and we're not going to withhold -- we need to know that what we're going to test is sufficiently effective, so that by not giving them something that we know is effective, that we're not putting them at inappropriate risk. And so that's the ethical challenge. And without labeling it, I guess I'm going to just suggest three potential steps. And remember, I'm an

ethicist at FDA, and so anything I say about trial design can be denied by anybody in the division. So, the first step might be to establish by equivalence. So, if you took some healthy adults, and you just gave them HRIG versus the monoclonal antibody, do you get a curve it looks the same. I mean, I think we do that. Cmax, half-life, et cetera. I mean, can you make the curve look the same. Now, what I don't know is, there is a difference in measuring levels versus measuring potency, because some of the slides that were put up about the impact on vaccines suggests maybe there's a difference potency. That would have to be worked out. Then the second step could be mimicking, in a simulated PEP environment -- in adults, again not in children, but in adults -- whether or not giving the monoclonal antibody versus HRIG or ERIG -- depending on the circumstance, may be ERIG is the better thing to do -- and the vaccine, whether you get -- again, at 14 days, I almost see that is more safety issue. Are you're undermining the efficacy of the

vaccine, and you could do dose range, and find out what level of monoclonal antibody would undermine vaccine, because you then see at day 14, presumably because the monoclonal antibody disappeared, and the vaccine has been less effective, et cetera. So, you could then find out. And so -- once you've got that mix, then this is the more controversial step.

DR. CONNELLY: And those were non-exposed (Inaudible)

DR. NELSON: Yeah, that's simulated PEP, simulated PEP. Non-exposed, no rabies, simulated. Then this gets more difficult. My own bias is I'm not sure you could design a superiority trial, and I doubt you could design a non-inferiority trial, not because you couldn't pick a margin necessarily, but because it would be so big that it would be very difficult to do given the effectiveness. And so, this is what I want to put on the table, that you would just, at that point, whether it's approved, as it is in India, or whether it's an accelerated approval in the United

States. The point is, you then require a registry approach, prospectively, of everyone who gets the monoclonal antibody plus vaccine, and you basically monitor mortality at an inappropriate interval -- a year maybe, you've mentioned a year. And then, you have to make a decision as to when you see a certain number deaths that appear to be rabies related, you then concluded that was a bad thing to do or not. And one final ethical point, I think the decision about how many deaths you'd be willing to tolerate, because there will be -- I mean, we saw PEP failures with ERIG and HRIG -- there will be deaths. That should be a decision made in the community within which that monoclonal antibody is being distributed, relative to the other policy issues about why that, from a cost perspective, a safety perspective, and availability perspective, et cetera, ought to be in that community. I think you may have a different tolerance for the effectiveness of that new product in India versus the Philippines versus Thailand. If ERIG is working so well there, but

they can't get it, and so on and so forth, the decision on that topic might be different from an ethical or a policy perspective legitimately between different jurisdictions. So, that is -- I'll just stop there. That's kind of where my head is at in listening to this. But I'm curious, I mean, if Tom can design a non-inferiority margin trial that can be accomplished, I mean, I would love to hear it, but I suspect it would end up being very, very big.

DR. SIBERRY: So, Skip, thank you very much. I think that frames it very well for us. I think, my guess is, that your first two points, the healthy volunteer bioequivalence studies using serologic measurements and the healthy volunteer mimicry of the regimen that would be used in a post-exposure prophylaxis setting, again, in healthy volunteers, to understand the potential impact on, say, vaccine response. I'm guessing those are rather non-controversial. But let me pause and make sure that, before we then delve into what I think is --

DR. NELSON: Let me make other point. On the third step, I think I would be willing to enroll children from the get go. You know, I just -- yeah, I'm just saying it -- so, I don't think you'd have to start giving it only to adults. I think there would be enough prospect of benefit based on prior too. But what I didn't hear is that in that Phase 2/3 that people were doing the dose ranging with monoclonal antibody. So I'm not sure if that was done in any of these programs, as opposed to just giving it and seeing what that day 14 is, and the dose ranging to see the impact on vaccination. That I'm not sure about.

DR. SIBERRY: So, should we take a minute and talk about that, the -- that -- because I think we can kind of dispense with that relatively shortly, and then really spend our time on Part 3. So ---

DR. NELSON: Can you concisely summarize the three steps, (Inaudible) ---

DR. SIBERRY: Yes, so the first is bioequivalent study, basically serology adult

healthy volunteers. The second is in order to assess the potential impact of the monoclonal antibody on vaccine response, again in healthy adult volunteers. Perhaps a dose ranging study of the different monoclonal antibodies, and then serologic response to vaccine measured at certain intervals after administration. I think those are Steps 1 and 2. Step 3 is where I think we will spend our time and, you know, Skip sort of said the current approach is already so highly efficacious, it's probably not possible to do superiority study. Then non-inferiority, even if we agree on a margin, but have a sample size of a gazillion, so probably not feasible. And so he proposed a, sort of, registry approach. That, again we can get into in more detail. Does that more or less capture your three steps? So, on the Step 2, I think I -- Skip just wanted a clarification about whether people agreed that we would need, sort of, a dose ranging study, rather than just one or two -- a dose ranging study to understand the right dose of monoclonal antibody

relative to potential impact on vaccine.

DR. WILDE: May I make a quick comment here?

DR. SIBERRY: Yes, please.

DR. WILDE: Let me bring you back to the real world, because you're not going to do the study here or in Washington, DC. You're going to do it in a country like Thailand, India, or Philippines.

DR. SIBERRY: So, I don't know that that's a given. Skip--

DR. WILDE: Well, it is, because when a patient comes in or a mother with a child that has just been bitten, they will know about this ---

DR. SIBERRY: Dr. Wilde, I just want to make sure we have time to get to this, but this is not about patients, this is healthy volunteers, 1 and 2. So, let's finish that, and then we need to --

DR. WILDE: Yeah.

DR. SIBERRY: -- address, I think, what you're getting at.

DR. WILDE: Well, that would -- yeah, that would (Inaudible).

DR. NELSON: And I would actually propose that Step 1 and 2 ought to be done in both developed and developing countries. I mean, we ought to be able to willing to pay people and ---

DR. WILDE: Healthy volunteers and I'm all about that.

DR. NELSON: Yeah, all right. In the first two steps.

DR. WILDE: We only dealt -- when we did (Inaudible), we only dealt with bitten and we would have had health (Inaudible).

DR. NELSON: That's Stage 3. That's Stage 3.

DR. WILDE: Okay, I'll shut up, I'm out of line here.

DR. NELSON: No, no, I'm just -- I know we have a lot to talk about. So, any comment on the dose response.

DR. MOLRINE: Yeah, this is Deb Molrine. I just wanted to make one comment. So, for the --

because of time constraints and also the Indian trial has not yet been published, and as this is a public meeting where all, you know, everything is given publicly, I think that -- you know, I think highlights have been mentioned and data, you know, will be forthcoming that everyone then will be able to evaluate. But in terms of what you're speaking about, I think many times Phase 1 studies are your simulated PEP. So, you are dose ranging your monoclonal antibody dose against your HRIG, and then a vaccine only control. So, in your Phase 1 study and healthy volunteers, you're doing post-exposure post-prophylaxis with simulated PEP to dose range, and find that dose of your monoclonal that is most comparable to HRIG. I mean, I think that's the point where -- at the moment what do we have, we have serological activity that's how old H, new HRIG products are basically found acceptable to the ones that were on the market. It's not done in terms of any type of mortality end point. But the fact that do you have comparable neutralizing activity. The gold

standard we have at the moment is the RFFIT assay in terms of what is on the market that we all agree is highly effective. So, in that case, a Phase 1 study does take into account your dose range, you know, the monoclonal antibody against your standard of care, and you find that dose and that you want to proceed to -- into your patient population. Coming into this meeting, it wasn't a given to me that we were only talking about monoclonal antibodies for the developing world, but also is there, you know, the possibility of rabies MAbs to be used in -- for different variants in different parts of the world like North America. And in that case I think, you know, your pivotal trial designs would be very different. I mean, it's very hard to have a mortality time, you know, end point. If you think the number of bites that are actually rabid, you know, the possibility without treatment that you might survive a rabies infection that if you look in the literature, you know, is a possibility, and combined that with 100 percent or 99 percent gold

standard, you know, your pivotal trial is 30,000 per arm. I mean, I would love statisticians to say it's much less. I mean, I think it's not -- it's not feasible. So, I think part of the discussion has to be for a pivotal end point that it may not be a traditional efficacy study where you're looking at mortality. And so, you know, can there be other, you know, markers. And at the moment what we have is serological activity, in terms of maybe -- being able to say that there is a new product that can be comparable to what's out there.

DR. SIBERRY: And I do want to come in to the second part of this top talk about the end points that we think would be most rigorous and acceptable, what people think. But in terms of the ethics, is there any question about what people feel about testing vaccine with placebo and vaccine with the new product in settings where RIG is not currently available? Is there any discussion about the unethical nature of that approach?

DR. WILDE: About ten years ago at the WHO Expert Committee, which I was a member. We, at that time, faced the same problem, and we made a decision which is in writing somewhere, that says that with rabies, you do not have to do efficacy studies anymore. Immunogenicity studies, solid ones, are sufficient because obviously, you know, we couldn't answer your question at that time either.

DR. SIBERRY: So, you present the WHO perspective that ---

DR. WILDE: Well, my own.

DR. SIBERRY: Your ---

DR. WILDE: But it's -- I think it's in writing.

DR. SIBERRY: Okay.

DR. WILDE: I was on the committee.

DR. SIBERRY: All right. So, and this is again getting to a mixture of end point and ethics, but argument for not having to have a mortality end point, but settling on immunogenicity end point as ---

DR. WILDE: Because we decided it was impossible to do --

DR. SIBERRY: Okay.

DR. WILDE: -- in most cases. That's it.

DR. TAYLOR: So, the proposal that you're making on the table is, would it be ethical to do a randomized control trial, testing the vaccine, plus ERIG or HRIG, against vaccine alone?

DR. SIBERRY: Vaccine plus monoclonal antibody against vaccine alone, in places where ERIG or HRIG aren't available.

DR. TAYLOR: So, I will say I think that's unethical, and then I can tell you why but ---

DR. SIBERRY: And that's what ---

DR. TAYLOR: If that's what you're asking.

DR. SIBERRY: That's what I want to hear, because that was sort of implied here. But I want to just, again around this table, see if there is any disagreement about that.

DR. FLEMING: Yes. So, what is the

question? The question that Sarah read at the very beginning was clinical development of rabies, monoclonal antibody for use in PEP to demonstrate significant benefit, for use as an alternative to existing hyper-immune globulin products. If that is the question, then I would argue yes, and you will be giving hyper-immune globulin in the control arm. If it's as an alternative, this is a setting where you're presuming that I could get the hyper-immune globulin, but I want to know whether or not the antibody could be used instead. So, I would agree that I would give it.

DR. SIBERRY: Okay.

DR. FLEMING: But if the clinical issue here is, there may be a significant cohort of people where they don't have access, it could be supply, it could be toxicity, it could be unwillingness to take it. Then in that setting, the true standard of care for those people would be the vaccine and wound cleansing, and it would be ethical and proper, because I've always argued that for given setting, the proper trial offers a

version of standard of care for that setting. And I wish I had five minutes to describe that. Fortunately, we followed that when we're developing HIV prevention, mother to child transmission interventions, in African and developing country settings, in the late 1990's, when we knew how prevent it in developed country settings, with triple drug therapy. We looked at single dose Nevirapine against a control that was available standard of care in that setting. And by doing so, we discovered it had profound benefit in that setting. If we had done a study that offered everybody triple drug therapy, as was done in the US, we would have shown that that had no benefit. And so, we would have violated distributive justice by using an intervention in a setting that isn't standard of care or a version of standard of care in that setting. So, what is the question? If the question is as an alternative to, yeah, I agree with everybody, you would give it against HRIG. If the question is, in people that don't have access to HRIG, then

yes, distributive justice I would argue, I would say, if we're using a population in Philippines that it doesn't have access, then the control should be what they have access to and find out if its superior.

DR. SIBERRY: Right. So, that then -- I think that ---

DR. FLEMING: There's one other quick point, and I can wait if you want me to wait, and that's the pediatric aspect of this. Should I come back to that later?

DR. SIBERRY: Come back to that, because I -- what I'd like to then -- Holly, you sort of state the case for why, that approach in your mind would be unethical.

DR. TAYLOR: Yeah, so I think I agree that the example of the short course trials in Africa and Thailand many years ago is an argument in favor of using a relative approach to defining what the standard of care is. My -- I think this is different, and the group can fill in. I think that the diffusion of this technology, meaning the

access to the vaccine and ERIG or HRIG, is very different than what the diffusion of the technology was at that time, as it relates to access to AZT for pregnant women with HIV. That, I don't think they are equivalent in terms of what is available. I think the barriers -- again as I understand the literature that was reviewed, that the barriers are related to things, like, you know, choices in terms of what different places are spending their money on, accessibility, willingness of people to actually show up at the clinic setting to have -- to be treated, et cetera. I don't -- I guess to say the diffusion issue is one that I think is different, in terms of that particular case.

DR. NELSON: Just one -- I agree with Holly. One other option I'd be interested in hearing from those that are working in these areas is, if there is a limited production -- I mean, I have no idea what one's production capacity is yet for the approved product, for example, in India -- if that production capacity is not yet up to meet

the demand, that might exist for PEP in that setting, one might consider taking bite clinics in doing a Cluster randomized trial. And that at least -- a little more complex. But it then takes away some of the consent issues, randomization issues, and some of the complexity that might exist in a center with patients coming through the door, and some go left, some go right, that sort of thing. So, if the production can't meet the demand even within that sort of setting, maybe a cluster randomized trial would be an approach that would try to address that. Just a thought.

DR. SIBERRY: Skip, maybe I can ask one of our representatives from the Indian setting or the Filipino setting or Thai setting, if you have had conversations like this about the availability -- the practical availability or not and how that might impact your decisions about ethical approach to studying this.

MR. GUNALE: So, in India, like, the latest survey is of 2003, which WHO sponsor, and the use of RIGs was almost three percent, three

percent. So, but that is quite old data now, and it varies. After that, there are some studies which have been published in non-index journals, which show in urban areas it is up to 60 to 70 percent, the uses of RIGs. Whereas in rural, it is 30 to 35 percent. But again, these are not very robust data. So, most of that -- and ERIG is supplied in many government hospitals, but that is again not all across India. But most of the states give you free of cost ERIG. Again, that happens in the district level or sub-district level settings. So, what happens at those rural levels, we are not aware. And the trials were conduction at the tertiary level hospitals. So, where the standard of care is ERIG, but again ERIG is not a consistent supply, it is not a 365 day supply. So, sometimes ERIG is available when the government has purchased, and the manufacturer has the stocks available. So, it is not a consistent supply, so it is --

DR. SIBERRY: So, in light of that ---

DR. GUNALE: -- equivalent to, like, non-

availability of the RIGs for the treatment. So, when the patient's presented, they have an opportunity to receive the standard of care as HRIG. In the normal case, they would have received the ERIG. So, they had one chance of receiving HRIG, or the other risk of taking a new non-prone therapy in those who were exposed. But the justification for that was a simulated PEP, had demonstrated equivalence to HRIG containing (Inaudible).

DR. SIBERRY: But the information you had about the practical lack of availability in a lot of settings, did that come up in conversation as justification to have placebo be the comparator, compare the -- your product against nothing since nothing was what was available.

DR. GUNALE: No, that would not be acceptable because --

DR. SIBERRY: All right, thank you.

DR. GUNALE: -- this is a fatal indication so --

DR. SIBERRY: Sure.

DR. GUNALE: -- no regulator or ethics committee would have approved this.

DR. SIBERRY: Again, I'm just provoking conversation here, so that we're clear about where things stand at -- yes?

DR. QUIAMBAO: In the Philippines, it's just the same as India, we will not accept placebo, because the standard of care, they are issued RIG. Whether it's ERIG or HRIG. And that -- and the program is trying very hard to provide ERIG for all the bite centers. Although, of course, we have supply issues, you know, when they pull out the (Inaudible) product, there would be a big supply issue in the Philippines, and we're just now starting to use other products from India or China, et cetera. But, at the moment, the standard of care issues RIG.

DR. GUNALE: Yeah, because other point is, if it's routine care, it might be happening. People are not receiving the RIGs. But as a part of clinical trial, it will be not be accepted.

DR. SPARROW: And just to reiterate that,

is that we also ran this through the WHO ethics committee, a couple of years ago, this question, and they said the exact same thing, that in a clinical trial setting, placebo control would not be ethically possible for rabies in particular. But I just had a question for Dr. Gunale, and that's about achieving informed consent for your Phase 3 clinical study, because it took you two and a half years to achieve enrollment of 200 subjects. And I know you had the interim review in the middle, and the DSM, the analysis. Did you have any trouble getting a -- achieving informed consent or were people willing to enter the clinical trial?

DR. GUNALE: The reasons behind the long duration of the trial was -- one was IMOGAM. IMOGAM was -- is not available in India, so it was to be imported from US. And the other issue was about several regulatory conditions that we were allowed to enroll only adults and post-menopausal initially. After submission of the safety data in December, we received the approval for pediatric

after almost eight, nine months, because this being the first time for rabies in India, so regulator used a very cautious approach. They did not want to take any risks. And consent -- so in November, 2013, the regulator in India started the process of audio-visual recording of the consent process. So, this is for the first time in the world where audio-visual consent -- recording of the consent was implemented, and these people who used to get surprise that why want to record it, and that was the reason that the screen (Inaudible) rate had increased, because the people starting saying that anyway then that it is fine, I would take ERIG from the hospital, rather than receiving HRIG and going through all these cumbersome procedure. Because the patient was bitten by animal and he was -- before receiving the treatment, he was going to get first audio recorded for the consent process, so ---

DR. NELSON: I just want to ask -- as part of your approval in India, do you have any obligation for follow-up in terms of mortality

after administration of this product as part of PEP.

DR. GUNALE: No, we did not have end point for observation of mortality. But for the Phase 1 trial, we had monitored the antibody titers for one year, and they were still maintained quite well about the 0.5. And for Phase 3, so our design was to follow them up until date.

DR. NELSON: No, I understand. I'm just asking now, in a post-market settings, sometimes the FDA will put a post-marketing study in place or registry type of thing, to follow up on mortality, for example, as a long-term outcome, independent of the short-term studies that you've already performed. I'm just wondering if there is any requirement for you to do that, or if you have any plans.

DR. GUNALE: It's not a mandatory requirement, but we could think of it.

DR. SIBERRY: Great. I think this has been a really helpful discussion about the ethical

issues around that sort of placebo controlled approach. If we manage to figure out, you know, how to go about studying this, what would be the appropriate point to include children? Skip talked a little bit about it. I want to give you first chance to talk to him about at what point children would come into this. We'll have Skip first.

DR. NELSON: Well, Holly put up, you know, our regulatory approach. I think it's a generally accepted principle in many areas, and the language may differ, where basically if you're going to put children at more than minimal risk or minimal burden, that there must be some prospect of direct benefit and so I think the point at which you begin to enroll children is when you've got some evidence that they would, in fact, benefit from that administration, and that's a combination of both benefit as well as risk. I'm interested in the fact that they wanted some safety data, which suggests that on the safety side, they wanted to see a bit more robustness on

that side before the risk and benefit was considered comparable. But that's the point. I might just say I personally would not do a simulated PEP setting in pediatrics, because there is no benefit from receiving the monoclonal antibody. There is a benefit of receiving the vaccine, but I think a simulated PEP ought not to be done in pediatrics.

DR. FLEMING: To do a pediatric trial, obviously, there would have to be some clear arguments that the questions that we're asking are of direct relevance to children. The temptation is to try to answer those questions in adults and then extrapolate those results to children. Certainly, there has to be particular care in the informed consent process when you have populations that would have cognitive impairment or children etcetera where the informed consent process would not be the same. However, to use those perspectives and be incredibly cautious and not engage children in the scientific process is a disadvantage to children. In fact, I was talking

to a pediatrician at one point who said they were sick and tired of having to use animal data to answer questions in children. I said, 'What do you mean by that?' 'Studies in adults.' So, an example of this, we studied extensively sildenafil in (Inaudible) hypertension and showed that when you look at various doses, that as you increase the dose, you get better hemodynamic function and that was their surrogate, just like our serologic surrogate, and in adults as you had higher doses and better hematologic, hemodynamic results, you did get better clinical outcomes in terms of six-minute walk. Children had the same functional relationship with hemodynamics. Ah, so, we'll extrapolate the adults to children using the surrogate. Fortunately, FDA had the wisdom to do a pediatric written request with a sponsor to study this sildenafil in children, which was (Inaudible). I was on the data monitoring committee, we terminated that trial where we found that with increasing doses in children, yes, you got better hemodynamics. You were getting a

fourfold increase in mortality. And so extrapolating results from adults to children and using surrogates like our all favorite surrogates here, like serologic measures, isn't necessarily in the best interests of children. They deserve to have an evidence-based insight about the best way to treat them as well. Clearly though, with great concern for the informed consent process.

DR. SIBERRY: So -- and I just would add since I also represent some of the pediatric perspective, that if you wait until efficacy is fully established in adults, then you often put children at a multiple year disadvantage to having the opportunity to benefit from that treatment. And so I think in many ways, that's why the approach is often as efficacy is -- often when it's Phase 2, looking good, and ready to go into efficacy trials in adults, that's the point where you begin at least do safety or PK or exposure studies in children, so that you don't have a huge gap in time between when children first get included. So, I do appreciate that you have to

look at in kids, I don't know that you always have to re-establish efficacy de novo in children. You know, especially for anti-infectives, if the disease process in children is similar to that in adults. I think in rabies it is. I think you could argue that efficacy of a product in adults would mostly require safety and dosing studies in children with some extrapolation allowed of efficacy. Holly?

DR. TAYLOR: So, I would agree, period. But I also think that it's important to think about, if we are going to include kids that we include enough kids, for example, to have the outcome of interest be statistically significant. To just throw kids in as part of that larger sample, I wouldn't be in favor of.

DR. SIBERRY: That's a great point, because so many times a lower age bound will be there, but when you look at enrollment, it's a tiny number who actually get enrolled in the pediatric age range. So ---

DR. SIBERRY: Yes.

DR. FRANKA: Can I ask here, Richard?

DR. SIBERRY: Yes.

DR. FRANKA: Just for clarification of terms. When you mentioned simulated PEP, you were talking about no exposures or non-bite exposures? So, there was no exposure at all?

DR. NELSON: Yeah, simulated PEP generally refers to no exposure, and you're just simulating the PEP as if there was an exposure.

DR. FRANKA: So, our discussion up to now is without any exposure to rabies virus, right?

DR. NELSON: Well, I mean, in the steps of the immunogenicity and the like, but -- I mean, there are a Phase 2/3 trial that was -- they were people who were bitten, if I recall. So, I don't know if there were children in that. They were try -- children after you had (Inaudible) --

DR. FRANKA: Children were (Inaudible).

DR. NELSON: -- safety. So, that's fine. It's the simulated component. Okay, thank you.

DR. FRANKA: No, I just want to clarify. It was not simulated, the children with exposure,

so it was actual PEP? Similar to in-simulated, we don't give a local infiltration. It is always systemic. So, it may not completely reflect the actual PEP where you infiltrate into the wounds, but it gives you confidence to go into the patient population. So, in simulated PEP, we give it systemically. And giving systemically is likely to interfere more with the early immune response to the vaccine.

DR. NELSON: So, can you talk a little bit about the -- in your trial, what were the requirements to enable to start enrolling children?

DR. GUNALE: So, our protocol from the beginning had inclusion criteria as dosage to more than or equal to five years and above. There was no upper age limit and why these children, these lower limit was taken, was because majority of the bites happen in children. So, this was the consideration behind including children from the start of the program.

DR. SIBERRY: But I thought that you

started enrolment in --

DR. GUNALE: No ---

DR. SIBERRY: -- non-pregnant adults in --

DR. GUNALE: Yeah, but -- yeah, so -- but the -- when it was presented to the regulatory, so regulatory opined that you first do a safety data, submit a safety data of ten adults to us, adults and post-menopausal women, and then you go ahead with the children. So, regulatory took a stance that first the -- though it was demonstrated in the Phase 1, the safety was adequately demonstrated in the Phase 1, still regulatory wanted that these are the potentially rabid-exposed population, so first let safety be demonstrated in adults, and then you go into the pediatrics.

DR. SIBERRY: With the idea that children suffer disproportionately from this disease, so they were to be included as soon as there was some safety data available from adults. There's a comment from down there.

DR. SCOTT: I just wanted to make a few comments about safety. So, with respect to the polyclonal hyperimmune globulins made on a certain platform, we have a lot of experience with them, and they are -- we know -- we understand their safety profile. Likewise, with respect to monoclonal antibodies, on the platform that's being used, or the type of platform and the type of FC and so forth, that's also probably reasonably well understood even in children. Okay, so I'm not sure that the safety concern is that similar to the one described for sildenafil. The other thing I just want to point is that it's very common to say that blood-derived immunoglobulins have a risk for infections. And while that has been historically true, since 1996, there have been none because of the advent of -- and regulation of multiple viral clearance steps for these products, so it's just another safety thing.

DR. SIBERRY: Great. Great points and maybe as we, kind of, shift into talking then more

about some of the clinical trial designs that people think, you know, in Skip's, sort of, framing beyond 1 and 2 when we get into the actual efficacy or clinical studies of the products on a larger scale, I do want to make sure that folks know -- wherever you're sitting, in the audience or around the table, you are welcome to stand up with your comment or question, so that everyone in the room is invited to participate here. Skip?

DR. NELSON: I'd like to follow up on the pediatric discussion. You asked a question of our colleagues from -- who have experience in the treatment of rabies. I was struck by your slides you presented from the Philippines, that when you presented the PEP failures four out of the five were children, and I'm just wondering in the epidemiology, the extent to which children could be at increased risk based on where they are located relative to the animal and so and so forth. If you see more PEP failures which might be an argument as well for early enrollment and enrichment and so on and so forth as we talk about

trials, if children are at higher risk for PEP failures for that reason, I'm just curious if -- I mean, it's some anecdotes, but I'm just curious if that's your experience.

DR. WILDE: Well, I was going to make the same comment that you made, actually. You know, the children are not only at greater risk proportionally of being bitten, but also of being bitten in dangerous places, the hands, the feet, and also, you know, presumably the virus may be more invasive. You know, into children's tissue, I've heard that argument. And I have certainly seen, you know, out of the 140 or so patients that we have had, a lot of them were children, and I think my colleague here from the Philippines will tell you the same thing, won't you? So, this is another argument to be more ready to do something with children. I felt that I just didn't want to talk too much anymore.

DR. SIBERRY: So, I think we've heard important arguments for why children need to be included early, less perhaps of a safety concern

for this genre of product and a real concern that children are disproportionately at risk perhaps even of some of the most severe consequences.

DR. WILDE: And don't forget that the parents know this in most of the countries we're talking about.

DR. SIBERRY: Indeed. So, if we try to delve then into the second part, into the clinical trial designs, so, if we assume that -- well, we shouldn't assume anything. So, if we've got a product that we can show produces antibody levels that we think are meaningfully high, and that don't interfere with a vaccine response in the healthy volunteer studies, what then? What would be the best way to test that product for us to then be able to license it or use it in clinical care of patients with high risk bites?

DR. CONNELLY: And if I could interject. I think that we also need to bring into this the totality of the information. So, even though we talked about it more in the morning, but the animal data and any cell culture in vitro data,

because as was mentioned in one of the earlier slides, it's critical that this monoclonal antibody dose is well-defined prior to entering into the not -- to the rabies -- suspected rabies exposed population because the clinically important end point we're talking about is death. So, to the extent that the panel can talk about not only for the clinical trial designs in the healthy volunteer population and what does that serologic assay measurement, what can that tell us about how -- what do those parameters tell us about what is most predictive for protection of developing rabies infection. I don't know if that's really been -- I'd like more discussion about that and what other parameters from the non-clinical data are important before proceeding with any trials in a suspected rabies exposed population. Maybe I'll start with -- okay.

DR. STYRTL: Barbara Styrt from Office (Inaudible). If you won't mind if I just kind of expanded a little bit on the question and see if we can -- some of these may be things we wind up

thinking about after -- as we reflect back on the discussion. But to try to link so the terminology that's been brought up at various times including some of Skip's proposals and some of the things discussed earlier, the whole issue of whether the number attached, we've heard that there are a number of different serologic assays we seem to be primarily interested in functional serologic assays the question of whether a -- but these are not the only ones there are. The question of whether a number attached to serologic assay result actually means the same thing if you were talking about polyclonal antibodies where presumably, your polyclonal reflects the entire repertoire of responses to rabies vaccine versus monoclonal antibody. Does it matter what's the virus that you're using in the neutralizing assay? We saw a table earlier where it looked like RFFIT done with two different viral strains gave actually remarkably different results, and would you need to see a range of those to be comfortable that you were looking at neutralizing activity in

serum in a generalizable way? And also does it make a difference when You're talking about the number attached to the serological result depending on whether you are looking at a level that was achieved in response to vaccine, in which case there may -- as has been mentioned be other unmeasured components of vaccine response going on that could be very important in protection, whether you're looking at antibodies. Dr. Wilde mentioned that if someone who actually was exposed to rabies and didn't get PEP manages to mount their own antibody response, that very occasionally that may be effective even when there is appearance of clinical disease. If you're looking at measurement -- a number attached to an antibody, an antibody measurement result, after passive administration where you may not have as much historical information about what correlates or what predicts protection in the long run. And then also whether the serum neutralizing activity or whatever you're able to measure after a blood draw tells you the same thing in healthy

volunteers getting the product IM, whether it would tell you something different potentially if you got the same measurements after someone got the antibody infiltrated at the bite site after a bite exposure, so that there are a lot of different aspects. And then for that matter, what it means if you have different antibody levels, how far out after your PEP regimen, having looked at some of the early Thai Red Cross studies, they actually were concerned that the vaccine response was falling off earlier than with the control they were using at that time and added a late booster to try to avoid that. Does anybody know where are the viruses hiding out in people who have long incubations and late disease presentation after not getting PEP? And, you know, what difference would it make if you had circulating antibody, whether you would know that falls off earlier or not, whether that would change the risk of late development of disease? So, these are things that -- not expecting answers or delayed discuss -- or detailed discussion of any of them today, but just

as things that might factor into some of the discussion of which kinds of studies are most informative in which kinds of volunteer situations.

DR. WILDE: I was trying to stay a little bit away from this, because, you know, you have to face that we're up against a real emergency now, okay? ERIG is insufficient in supply. There are only two licensed or recognized manufacturers right now, and they are not producing enough because people aren't buying it, and they are not distributing it where it's needed, so it's not available. And that's a problem we will have to overcome too. But it creates an emergency. We don't treat people with the immunotherapy who need it. The second thing is that a lot of the questions that you raised, we have no answer for. We don't really know where the virus hides, that incubates for seven years like we've had. You know, we identified the virus, it was picked up in the United States seven years later as the Asian strain, they sent the sample to us. So, there's

no question about it. It is able to go into a non-reproductive mode in some fatty or hidden place in the body. But this is extremely rare, and we're not up against it, we're up against an emergency. HRIG is not available at all outside a private hospital in Bangkok and the same, you know, it's true in the Philippines. So, you know, these are real emergencies, we need this product and we cannot make the study so complicated that it answers every other question that we would like to answer. So, that's the first thing we have to understand. And I think we have to work along with it. We did all these immunogenicity studies, you know, for FDAs. Not your FDA, but the English one, the European one, (Inaudible) was the first one which is one of the most commonly used vaccines now. And we prove that by picking a couple 100, 200, 300 people, I forgot how many, but the paper is in the box, you know, that I supplied and others supplied. You can look it up or you can go onto Google or (Inaudible). And we had a few hundred people, a variety of people, we

excluded some, we excluded pregnant women, which we had to, and probably we shouldn't even, because we had enough evidence from non-official studies. You know, we saw so many patients, we saw 40, 50 new patients a day, and you do the same thing, still, in the Philippines. So, we had, you know, observational studies, and anyhow, we took 100, 200, or 300 patients, we did antibody titers on them to make sure that they were truly immune to rabies, and some of them turned out not to be, and grandmother told them. So, you know, we did those and then after we had antibodies, we took a titer on day -- I'm not quite sure whether it was Day 7 or Day 14, because we were interested in the, you know, long-term value of the vaccine. And then at the end of it, these people were either alive or they were not and almost all of them, the way I remember, were alive. And we did an antibody titer on them, and if it was low, we gave them a booster and saw whether they had an immune response. And as far as I remember, all of them did and that ended the study. That was it. Why

can't we do the same thing --

DR. SIBERRY: Okay, so we have --

DR. WILDE: -- and get done with it.

DR. SIBERRY: -- a practical proposal in light of the urgent need. Ed, comment?

DR. COX: Yeah. Hi, Ed Cox, FDA. So, just a quick one, not on the proposal, but more -- I'm wondering, you know, we're sort of in the land of, you know, not really having the data that we'd like to have to understand a lot of the different things that we're doing here. Is there any insight into how ERIG compares to HRIG with regards to its effect as part of a post-exposure prophylaxis regimen? I'm trying to figure out -- you know, we talked about how hard it would be to beat, you know, HRIG plus vaccine. I'm wondering about ERIG plus vaccine. Are there any insights into how ERIG performs?

DR. WILDE: There are thousands of cases now. You know, look at the data.

DR. COX: Yes, it ---

DR. WILDE: People have published papers.

DR. COX: So, you think ERIG will -- there's no deficit with regards to the therapeutic efficacy of ERIG compared to HRIG.

DR. WILDE: Well, (Inaudible). Again, these are not done studies according to your and our also --

DR. COX: Right.

DR. WILDE: -- the desirable requirements. But there are thousands of patients that have had ERIG and there are thousands of patients that had HRIG here. There are very few in developing countries have had HRIG and vaccine and they all seem to survive with a few exceptions ...

MR. COX: Yeah.

DR. WILDE: -- and I have been collecting failures and you've been collecting papers and writing papers -- you know, publishing papers on this. Usually, and not always, you find a reason. One reason is that you've missed a small wound. The patient has horrible wounds on the legs, on the hands, and you don't undress them in an animal

bite clinic and there is a scratch on the back. Stuff like that happens. And the others, of course, are obvious. We don't inject the wound properly or the virus has already found itself a home in a nerve. So, there are these things and some of them, you don't know, but they're very few. We can start saving lives by bringing immunotherapy to the country where it's needed.

DR. COX: All right, and ...

DR. WILDE: It's no problem here.

DR. COX: And the reason I'm asking too is -- I mean, some of the discussion around non-inferiority and the difficulty of actually trying to figuring out what the non-inferiority margin is, you know, we talked about the challenges of trying to show superiority. So, I'm trying to figure out if there's a way to somehow get to some, you know, clinical trial that will help, you know, in interpreting the effects here.

DR. WILDE: We've talked about that for hours at meetings, you know, in countries like Thailand. There -- I don't think, you know, as a

clinician -- I'm just an old country doctor from Alaska, basically, originally. And so I think, like, you know -- like, she does too. And we don't know. There is no way you can figure out what happens in the wound.

DR. COX: Okay.

DR. WILDE: You can stick needles in, you can do biopsies, and this is all crazy.

DR. SIBERRY: Maybe just one.

DR. WILDE: Makes no sense.

DR. COX: Okay, one more time.

DR. WILDE: We got to go and get done with this thing.

DR. COX: Okay, thanks. And I think we all do want the same thing. I mean, we're trying to figure out how the products -- you know, a new product would work and, you know, we're depending upon it to, you know, prevent death, and it's always tricky. What are the sort of things that we can measure and are the things that we can measure -- are they going to help us to get to that conclusion or are there still gaps out there

with regards to, you know, what we're actually learning about a product and whether it will actually (Inaudible) prevent death?

DR. WILDE: Well, the only way you can do it in the wound, which is we all want to know this, you know, is in animal experiments, which may not apply to humans. They often don't. And even there, it will be difficult to do and you would have to do multiple biopsy of the wound, and that itself would endanger the patient.

DR. COX: No, no, I appreciate your comments, Dr. Wilde, and that's what I'm trying to figure out. I mean, if you -- so where does that put the product? I mean, if at the end of the day, you still have uncertainty with regards to how it would perform, would it be a product that you would essentially use when you didn't have other options because of either supply issues or refusal to take the other product? I'm just sort of curious, you, as a clinician, where you might position such a product.

DR. WILDE: Well, what you do with other

things is do a post-marketing study. A very elaborate study with lots of lots of people and you see what happens to them, which means that you have to keep good records, not more tests. You need to study the patient, look at them. You know, these are things that you have to do.

DR. COX: And this matches --

DR. WILDE: That's how you're going to solve it.

DR. COX: -- a little bit, Skip's idea for sort of that post-marketing or registrational approach. Could I get to Holly and ---

DR. SIBERRY: Yeah, please. I was going to -- and I was going to ask too --

DR. COX: I'm sorry.

DR. SIBERRY: -- maybe we'll come back to what the design of that study might look like too.

DR. COX: Yes.

DR. SIBERRY: That would be helpful.

DR. COX: Yeah, that is what we want to get to because I think that would be important. Holly?

DR. WILDE: Well, there are other people here that are more knowledgeable of the design studies.

DR. TAYLOR: So, it sounds like the current challenge, the current emergency as described, is that it's a supply problem, that there are not -- there is not enough RIG to go around. I don't have in the materials that were shared or that I read -- can someone say a little more about how the mAbs will overcome -- I mean, is it nearly a cost of production that it's cheaper and therefore, the country made -- right, I mean, it still relies on the individual countries making a choice about whether to invest in the new thing or the old thing. And is it, like, grand scale differences in terms of cost to say -- I mean, if it's a dollar per person for a RIG, is it a penny per person for a mAb? Does that mean Thailand would buy a hundred more mAbs than RIGs?

DR. SIBERRY: So, this is a great question because in some ways, the ethical

underpinning to the whole purpose of studying a product, which we think would be as good as, not necessarily better than the existing product --

DR. TAYLOR: Is that it's going to get to where it needs to go.

DR. SIBERRY: -- is because we think it could make it more available to where it's most needed. So, do we have reason to believe that that monoclonal product would be affordable and available in a significantly better way than the current product?

DR. COX: (Inaudible) come up with the answer.

DR. DESAI: Well, I think the question is two-pronged, affordable and available. And one of the challenges with availability of ERIG or HRIG indeed is not necessarily only the cost. It's also the scalability of production.

DR. TAYLOR: And that's exactly what I want to hear about why is -- how much easier is it to make the mAb than it is to make the RIGs.

DR. DESAI: Well, clearly, monoclonals

are manufactured using the component technologies and are commercially scalable. We have significant experience with commercializing monoclonal antibodies in the world, and it's far more scalable commercially in terms of meeting the increased demand, if there be any. Coming back to the question of affordability, I do believe economies of scale would drive that particularly level. However, as Dr. Wilde, in his presentation, I think posed a challenge to the industry saying that unless it is as cost effective or more than ERIGs, it might find it a challenge to get adopted in public health programs by various governments. So, clearly, there is a benchmark that is available for the industry to follow. However, I think, and I come back to the same question, the advantage with monoclonal products would be to -- A, would be scalability and B, would be more batch to batch consistency, which is something that you miss with serum products whether you're talking about an HRIG or an ERIG. And essentially, the risk of known or

unknown infections, as we keep talking about, also gets addressed with monoclonal antibodies. So, these clearly are the -- I mean, just to answer the questions about affordability, accessibility.

DR. WILDE: (Inaudible) and the Thai Red Cross who manufactures ERIG and I told them in advance, 'You're going to be out of business one of these days.' And he says, 'Thank God,' he says, 'We're losing a fortune on ERIG'. So, I don't think you're going to have any serious opposition. This is one of the good things.

DR. SIBERRY: So, if efficacious scalability and reproducibility are real advantages, it sounds like price is a question with some hope. And WHO maybe -- I don't know if you have any comments on that, but often finding ways to help us work on getting pricing rights.

DR. SPARROW: Well, I think the current -- with current monoclonal antibody production methods, the average cost is about 100 US dollars per gram of monoclonal antibody. However, it's a very little amount of monoclonal antibody that is

needed for rabies post-exposure peripheral access. So, you're looking why, why, why we are into the, you know -- I think tens of milligrams, is that correct? So, already, that's much lower than, you know, looking at how expensive monoclonal antibodies, (Inaudible), and these kinds of diseases where you need a lot of product to be injected. And then production costs are coming down with new technologies, so we're going to see, I think in the next few years, a dramatic full immunized production cost to begin with. I just wanted to say something. I thought that what Skip said earlier was very pragmatic about simulated PEP and then having some sort of a post-market surveillance commitment. And actually, this is what was done for -- is it Favirab? The Fab fragments that Sanofi passed or licensed in early 2000s. They did two trials, one in Thailand, one in the Philippines. The trial in Thailand, I think, was a Phase 1 that enrolled 25 or 30 subjects, and then the Phase 2 had 70 something subjects, which was in the Philippines. And that

was the basis. There was no dog bite victims, it was just healthy adults. And that was the basis for the approval with the French Regulatory Authority. And that wasn't that long ago, that was 2000 or 2001. So, that was sort of a leap of faith, I think, although it was, you know, an equine product that -- but it was a new equine product.

DR. SIBERRY: Was there a requirement for post-marketing surveillance that ---

DR. SPARROW: Yes, yeah. But I'm not sure what that requirement was.

DR. SIBERRY: So, let's go back to that ...

DR. WILDE: Yeah, it was ...

DR. SIBERRY: Ed asked about that and Skip proposed this, but let's -- what about this concept that -- of a post-approval approach, some kind of study that looks at after it's undergone some basic evaluation to -- instead of a conventional trial design. Skip, what -- do you have a sense of what that would look like, what

you had in mind?

DR. NELSON: Well, in effect, you're basically prospectively collecting data on individuals who get PEP with the new product and you're comparing it against the historical control, and so you'd need to look at all of the problems associated with making comparison to historical control. Now, some come into mind. I mean, my impression in listening to the clinicians here is a large part of the success here is a function of your skill in infiltrating the wound and has -- probably has nothing to do with the skill in giving the vaccine, which I could probably do, and other factors. And so I'm presuming you would then perhaps need to look at experienced centers and the experience there as compared to your historical control. And then as you roll this out, if it becomes more available, you'd have to look at new centers and their experience and you might expect that there could be a higher failure rate, potentially, as they begin to learn how to use this if they haven't had

much experience. So, it's kind of -- you'll have to then pay close attention to that and to the educational, I mean, programs, et cetera, if you have more of this and people are giving it where they haven't had anything to give before. So, bottom line is yes, I would be complex, but effectively, it would be accepting a historical control and I realize that that's -- got lot of issues with it, but I'll just -- that's what it would be.

DR. SIBERRY: Ed?

DR. COX: So, just thinking about this and, you know, just reflecting on some of what we've heard about, you know, vaccine -- or, I should say post-exposure prophylaxis failures, it seems like there's always, you know, some plausible explanation that comes up. You know, patient started too late, patient showed up, you know, at the clinic at a point in time when they -- it was too far, you know, the wound wasn't infiltrated well. So, it does make some argument for randomization in something like this to try

and be able to have two comparable groups so that you wouldn't be dismissing cases and saying, you know, there were some other reason. So, what about something large, relatively simple, and randomized in trying to do comparisons? And I think there's one other question that sort of follows that too.

DR. NELSON: Well, do you have enough ERIG to do that and then the question is what's the -- I mean, then you're getting into the non-inferiority margin and all sorts of other things to say that it's the same. I mean, it just strikes that -- if that's feasible -- yeah, you're right, you eliminate that bias, but ---

DR. COX: See, I don't think you get away from that by doing a historically controlled trial. I think it's just worse.

DR. NELSON: No, I'm not -- I'm --

DR. TAYLOR: I don't think it's worse.

DR. NELSON: -- I'm not saying that it's necessarily a great solution.

DR. COX: No, but I mean, the

historically controlled trial, you're not even -- you're going to be making comparisons with a group that's more distant, so I think it's going to -- it has a potential to sort of -- if there is a problem, it would probably be even less -- it would be more difficult to declare that there is problem with the new product because -- you know, unless you had very strict rules ahead of time, you know, there probably will be explanations as to why the product had a deficiency and --

DR. NELSON: Well, so I --

DR. COX: -- you wouldn't have a concurrent group whether that's true or not.

DR. NELSON: -- have an adjudicated case committee that looks at it and that sort of thing. I mean, it's not -- I mean, I'd be interested to hear whether a non-inferiority trial, looking at a comparator of ERIG, is doable. I mean --

DR. COX: Right, so ...

DR. NELSON: -- can it be designed and what would be the number? I mean, it strikes me that it would probably be very high --

DR. COX: Right, but ...

DR. NELSON: -- but I could be wrong.

DR. COX: Yeah, but I mean, I'm just -- you know, we've talked about how you can't really develop a non-inferiority margin and just -- it seems like doing a series of cases without a comparator would be even more difficult to interpret in some ways unless you had a strict rule of if, you know, there's more than, you know, one or two deaths in some large number of folks, then that would be unacceptable, which, you know, could -- it could lead you astray either way depending upon, you know, the actual patients that were enrolled in the trial. That's why it just seems important to have some metric even though you're not able to define a non-inferiority margin. That's why it seems like randomized in having compared -- but I welcome other folks' thoughts on that.

DR. TAYLOR: What would you -- so, it feels like you're saying that it would be randomized and non-inferior, or are you proposing

something superior?

DR. COX: Right. So, we talked about how you really can't define a non-inferiority margin, but if you're just going to do historical control, I think you're going to be even more in the dark.

DR. TAYLOR: But I guess I just want to push on what this randomized --

DR. COX: Sure.

DR. TAYLOR: -- controlled trial would look like and what would you do at the end and how many people would you need to enrol and how much further along would you be compared to doing the historical control?

DR. COX: Right. So, just so we don't get lost, those same questions exist if you do a historically controlled trial.

DR. TAYLOR: Yeah, no.

DR. COX: So, I think that's really what -- I think that's what the group was trying to figure out, what's meaningful and what would be considered a deficit?

DR. TAYLOR: But what would your

randomized clinical trial look like?

DR. COX: So, you'd probably randomize to whatever the existing standard of care is versus the new therapy. And then you would be looking for some ---

DR. TAYLOR: Let's assume it's --

DR. COX: -- you know, difference between the two groups.

DR. TAYLOR: -- ERIG versus mAb.

DR. COX: Sorry?

DR. TAYLOR: So, for example, we're saying vaccine plus ERIG compared to vaccine with mAb?

DR. COX: Sure, yes. That -- you could do that design and you'd be looking to see how the two compared. And rather than comparing it to a historical control, you'd do something randomized.

DR. TAYLOR: What's your tolerance then for number of deaths in either (Inaudible)

DR. COX: I was hoping you guys were going to answer that for us. See, that's the heart of the issue. But I think doing that as a

historically controlled trial, you're even more in the dark and therein lies the problem. And that's why the discussion, you know, of this problem is so difficult because we don't actually have a non-inferiority margin that we can define and then the question comes up of what is an informative trial. There's another part to this I think that probably is worth mentioning and that is, you know, based on what we are able to do, you know, with a new product, I mean, that will lead to some uncertainties, so will this trial be (Inaudible) or would this be -- you know, would you take that into consideration in the trial that you do post-marketing?

DR. NELSON: Cathy, Catherine?

DR. WILDE: You know ---

DR. NELSON: Hold on, I think she had a hand. We had a hand here, hold on. One sec, Dr. Wilde, we'll come to you. Catherine had her hand up.

MS. BROWN: So, I mean, I just wanted to say that, you know, I think at the beginning of

the day, we talked about the fact that we don't even know how many rabies deaths actually occur worldwide. I don't know that we actually know how many PEP failures occur and we certainly don't have any denominator data, and so I would really question the whole historical control when you don't know how many doses you've actually administered, how many people you've treated, and then how many failures you have out of that. It seems to me that you have to actually do a side by side, sort of, prospective moving forward.

DR. NELSON: Thank you, Dr. Wilde.

DR. WILDE: Well, you can control it a little bit and you have to. First of all, what you say is 100 percent correct and the other problem, of course, you have is not that we don't know, you know, what's really going on out there in the world. We also don't have diagnoses on the dogs. It used to be everybody almost brought their dog in because we use (Inaudible) vaccine 14 or 17 shots. People are scared as hell of having it. So, they found the dog, killed it, brought it

in, and it took us three hours to do simple FAT. So, this was easy, but it's not because they don't need to. They get all the shots and they feel confident that that's going to save their lives. So, that's one thing you cannot count on. So, what they are doing, they call it -- what is it? A verbal autopsy in India, that's a new term that crept up. You know, you take a history and if it sounds like it, then it becomes a verbal autopsy. That wouldn't fly, you know, when you're writing a paper. But one thing you can do, and I think you already suggested it, you do the studies in a couple two, three places where you can trust the staff, the Thai Red Cross Institute is one of them, and in a Sunday or Saturday, the Chulalongkorn emergency room because we control what's going on there, but -- and the same (Inaudible) institute and then you pick someone like Bangalore where they have a very good team of people that I think are trustworthy where a senior person is going to review the chart and look at the patient and get -- if it's a dubious case, get

the patient undressed, which is not easy to do in India, no problem in Thailand. But in India, you know, that's a big problem, so you miss wounds. So, you have to eliminate all this and you come up, I think, with a pretty good situation there. As far as autopsies are concerned, we developed -- we didn't develop. I don't know, some guy a long time ago in China probably developed it. But we publicized it and one of -- actually, our virologist does it. She gets a liver biopsy needle from the gastroenterologist and doesn't give it back to them. And she goes down to the morgue and she sticks the liver biopsy needle through the epicanthus of the eye. And I promise you, if it's done properly, there is nothing to be seen, so they don't often -- don't even get permits, they just do it. And you stick the needle in and you move it around and take a couple samples and you have a positive. They're very, very sensitive to do.

DR. CONNELLY: I just had a follow up. So, what I heard is that -- and from the

literature that there is a lack of information about how many people fail PEP -- lack of denominators. With the experience of people around the table, is there any data from any centers that is not published that ---

DR. WILDE: You mean data what?

DR. CONNELLY: In terms of how many people -- of the failures, what are the denominators?

DR. WILDE: You mean, how many people die of rabies proven or ...

SPEAKER: PEP failures.

DR. CONNELLY: Of all the people who are receiving ...

SPEAKER: (Inaudible)

DR. WILDE: PEP failures? No, because a lot of them are not reported because the doctor has no incentive to report it.

DR. CONNELLY: We just wanted to make that point and --

DR. WILDE: That's just one factor.

DR. CONNELLY: -- invite, if people had

their particular center experiences --

DR. WILDE: No.

DR. CONNELLY: -- to learn from that.

DR. WILDE: The isolated reports, I wrote three or four of them. Maybe more, I don't know. And my gang reported that people didn't report, you know.

DR. NELSON: But I think that that's ...

DR. CONNELLY: There are people that don't report.

DR. SIBERRY: Right, so it highlights that we --

DR. CONNELLY: Right, we lack that.

DR. SIBERRY: -- we lack that data, which could be very informative, but isn't readily available.

DR. WILDE: You're not going to get it.

DR. SIBERRY: We might not get it. Skip?

DR. WILDE: Don't dream.

DR. NELSON: Well, one comment and then an ethics comment. So, if there are no historical controlled data I, in fact, withdraw my suggestion

to do a historical control trial. But I was assuming that, at least at some centers, they would be able to have those data, but if they don't, then that's off the table. From an ethics perspective, I think an RCT between ERIG and a monoclonal antibody would be attractive. I think the devil would be in details as well because, let's say, there's variation and availability, I would -- you know, you have to decide. I would still give whatever products in the pharmacy to an individual who arrives, unless there's no product, and then perhaps if it happens to be a monoclonal, give them access to that outside of the trial. And the other question is whether or not you do that as a post-marketing and do -- I don't know if India has this and I'll just say this, whether or not, based on the Phase 1 and 2 data, one could do a accelerated approval based on a reasonable probability of predicting outcome and then allow it to be marketed, but then do the post-marketing trials. So, at least you're able to sell it and that would impact on the viability, I think, of

the company and so on and so forth. So, I think there's different ways to try and be creative and still end up with the RCT and not necessarily have the placebo be an issue. So, those are some thoughts that I think I would just throw out around the actual process, and pre-market versus post-market, et cetera.

DR. SIBERRY: So, if the RCT were designed as you said -- Tom, maybe I'll ask you. What would that look like? Would the end point of interest be mortality and what kinds of numbers would you need to be able to say something meaningful? I'm not going to even say superior or inferior. Something meaning meaningful about the result.

DR. FLEMING: So, I've been -- I'm struggling greatly with this. It's an inherently extremely difficult situation. I'm not convinced that there aren't settings where the vaccine and wound cleansing wouldn't be a proper control. We've been through that discussion. But if in fact there are cohorts for whom that is -- what is

available to them, then that is a proper control and that is a superiority trial and that is exquisitely understandable, interpretable. On the other hand, if there are no settings in this world where people don't in fact, as standard of care, have ERIG, HIRIG, then I'm all with -- if that has to be the control. So, if that's the control, then essentially, the issues that are on the table are is it a biomarker endpoint or is it survival? So, is it a neutralizing antibody end point or is it a survival? Is it a non-inferiority trial or superiority, and can it be non-randomized or randomized? I'm hearing those three things. I used to talk about my worst nightmare being non-inferiority trials with biomarker endpoints. I have a new one today, it's a non-inferiority trial with biomarker endpoint without randomization. That's what I'm hearing. And basically, what I'm trying to understand -- and I know this is incredibly difficult, but I'm looking at data that I'm hearing that says we have 16 million cases a year of patients that are getting access to PEP

and we are -- we basically have 55,000 to 100,000 deaths. My huge -- so -- and I'm impressed and pleased with the concept that monoclonal antibodies could be a step ahead in terms of scalability, lot-to-lot consistency, cost, but not if we lose efficacy, and I'm not saying we will, but not if we do. And you don't have to lose very much to double this number of deaths from 55,000 to 100,000. Basically, if you have one death per 300 people that are getting PEP that wouldn't otherwise have occurred, that's going to be doubling the number of deaths worldwide with our best intention of making monoclonal antibodies more widely available. So, if we're saying head to head against --

SPEAKER: (Inaudible)

DR. SIBERRY: -- against HIRIG -- head to head with a control regimen that would have HIRIG than HRIG, then fundamentally, that means to me we have to be similar to it. This is a population of people for whom that is an available standard of care and we can't be meaningfully worse. That

does mean non-inferiority. Now, if it were on survival, we're talking -- as would -- it would be a superiority trial, would be 20 to 70 deaths if it were a survival endpoint, 20 to 70 deaths by my calculation. That means it's 1,000 to 6,000 people. It's not a small trial, but it is in fact giving us a direct answer on, if we're going to replace HRIG by monoclonal antibodies, it would be giving us a direct understanding about relationship with mortality.

DR. SIBERRY: Two-thousand to 6,000 total for a two arm trial?

DR. FLEMING: Yes, and obviously, it depends a bit on the NI margin and it's untargeted -- in my view and all the queries that he's been making and we don't have an evidence based NI margin, i.e. we don't directly know what HRIG itself is doing on mortality. So, we would be postulating without knowing that it is in fact making a difference. So, that is a -- that's why, if it were the case that there is a population in the world that it doesn't have access to HRIG,

then that will be called placebo control trial, it would be exquisitely more interpretable. But if that doesn't ---

DR. MOLRINE: Sorry, you're assuming every exposure was a confirmed rabies exposure in that case?

DR. FLEMING: No, no, I'm not. And that's one of the advantages of the superiority trial is a non-inferiority trial actually unfortunately rewards ---

DR. SIBERRY: Hold on a second. I think you mean in the 6,000 arm to arm non-inferiority?

DR. MOLRINE: That was ---

DR. FLEMING: No, I'm not. No, I'm not. No, I'm not. And it's a great question. My preference for superiority trial, is it rewards rigor? It does, in fact, encourage us to make sure that we have a large representation of people who truly are exposed and that that they are treated early enough that HRIG would in fact have an effect. Because in a superiority trial, you're reward by showing a difference. Non-inferiority,

you're reported by not showing a difference, which is making -- attempting to be very flexible about letting people in who maybe aren't in fact truly exposed or maybe in -- so, in fact, so is the historical control. Let's go out and treat everybody under the sun because if they are not exposed, they are going to survive. So, these are issues and others have already said it that, because of the heterogeneity and the uncertainty, we must randomize. We must randomize unless you are willing to take the risk that we're going to more than double the number of deaths. Even with our best intention to get more access, we could double the number of deaths unless you think HRIG doesn't work. So, if you think HRIG works and there is heterogeneity, we must randomize. We can do a non-inferiority trial, but there is some treacherousness there because it does reward sloppiness and because we don't really know what HRIG's contribution would be. But if you tell me the world only has people in it where HRIG is standard of care, then I'm with you, we have to

give that as the act of ...

DR. SIBERRY: So, loud and clear, Tom, we got you, that you're making the case for a superiority trial with a placebo control ...

DR. FLEMING: Unless -- practically, I'm with everybody else. If that -- if a population doesn't exist where that standard of care -- then it must be HRIG. If so, non-inferiority. If it's non-inferiority, we need to keep the margin at a reasonable level, it needs to be randomized, and quite frankly mortality is a better end point. it could be neutralizing antibodies if you tell me that you know how much loss of neutralizing antibody is in fact acceptable without compromising mortality, which means not only you telling that you know that this is a validated -- not just a correlate of risk. It's a surrogate of protection.

DR. SIBERRY: First response.

DR. FLEMING: I call it a super surrogate because I not only know that the effect on neutralizing antibody predicts an effect on

mortality, I can tell you how much loss of an effect on neutralizing antibody is in fact tolerable without losing mortality. And by the way, that's at what time, at what magnitude. Come on.

DR. SIBERRY: But I heard a question of -- when you sample size a calculation, you must have been assuming some proportion with actual rabies exposure among all of those enrolled.

DR. FLEMING: Enough so so that we'd be looking at an overall risk of death, it would be under the vicinity of one in 2000, so 0.995 survival against 0.98 survival as an example.

DR. SIBERRY: So, that might have implications for the type of wounds, the location of wounds, right?

DR. FLEMING: I'm with you. And I'm frustratingly with you because the superiority trial would be pristine. The non-inferiority trial I at risk, but as everybody's saying, if the whole world has HRIG as their standard of care, then it has to be that.

DR. SIBERRY: Somebody was at the microphone before, I'm sorry, I didn't -- I took so long. Would you like to ask your question?

DR. KLEMPNER: I stood only because I think that there's five minutes left in the discussion and so I want to bring it back to reality a little bit. My name is Mark Klempner, I'm the executive director at MassBiologics, who holds some of those patents and et cetera on these ...

DR. FLEMING: Speak up a little bit.

DR. KLEMPNER: Is it the location of the microphone? So, this is a very interesting discussion that has really, in large part, talked about the development of a monoclonal antibody for international use. I have heard almost nothing about what it would look like as a path forward and guidance in the United States. And what's lost in the discussion is the complete difference in the epidemiology of rabies in the United States compared to the trials that are going on internationally and the disease that is seen

internationally, right? So, the CDC could tell us how many doses of PEP are administered in the United States every year. It's about 40,000 -- 35, 40,000? The cost that we charge -- we don't, but the cost for HRIG is about $3,000.00 per dose, per regimen. That's -- those are real numbers. The cost of goods for that, I don't know, but I do know the cost of goods for making a monoclonal antibody. It's way less than a tenth of that, so that we know that the cost can come down of that. There's very few PEP administrations in the United States percentage-wise that infiltrate wounds because the -- 90 percent of our exposures are bats and often there's not a wound to infiltrate. So, we're really talking about a very different -- there is no ERIG available in the United States, so you really are only talking about a comparison for HRIG if you're going to do something with a monoclonal antibody. There are no deaths, there are no HRIG, PEP failures in the United States. I don't know, maybe if there has been one, I don't know if there's any. I don't think that there has

been any in maybe in my lifetime for HRIG properly administered, post-exposure prophylaxis. So, it's not possible to actually do a randomized trial in the United States. I think that we have to acknowledge that if there is a path forward in the United States for an alternative to the serum product, which is HRIG in the United States, it's going to have to be a bioequivalent serologic markers study because there's not an alternative to that and we've presented to the FDA and others a model of what -- a superiority or a true randomized efficacy trial, you'd need -- I think Dr. Molrine alluded to at about 30,000 people in each study to -- 30,000 in each arm, I think is the number that we put forward. It's just not feasible to do those and I think that the FDA's agreed with that. So, it would be very helpful to have a discussion of is there a pathway in the United States for doing a trial in the United States for approval of a product for use in the United States to replace HRIG?

DR. SIBERRY: All right, great. Thank

you very much.

DR. WILDE: He's got a very good point and our new president may cut you down anyway. This is not America first.

DR. SIBERRY: There are only certain things in my control, so -- but I do think it is a good point and I don't know if anyone wants to make a comment on it. Yes?

DR. COX: So, I'll just -- so, it's never a good idea to get, sort of, regulatory advice for a particular product from somebody at a podium, so I'll start (Inaudible). There's always a lot of complicated issues, but when you -- if you do look across, you know, approved products and you move across something infectious disease areas, you know, we are able to use data from trials that are done outside the United States. Take, for example, malaria. So, you know -- and you've heard some of the discussion here where we've talked about some of the things that we need to think very carefully about if the design of a trial is a non-inferiority trial where you may

want to, you know, make -- you know, try and enroll patients who are at higher risk where there's a defined exposure. So, I think there is a lot of things to think about as we think about the trial design that would be informative for how the product works against rabies. And we heard some discussion earlier today about, you know, the different strains of rabies virus, so we'd need to think about how data acquired (Inaudible) might inform on how the product might perform in other patient with rabies in other geographic locations. There's a lot more that I think we could talk about. But you know, the goal here today is to talk about pathway four studying product for rabies in general and that's both, you know, recognizing that these products would have value globally to the patients out there who need new therapies. Then also potentially here in the US depending upon how, you know, precisely we can understand safety and efficacy and what the implications are, you know, given that in the US, HRIG is, you know, commonly used in standard of

care. So, I'll stop there, but we're certainly happy to talk more.

DR. SIBERRY: We did agree that this product in its healthy volunteer studies could take place, at least in part, in the US. I don't know if the ethicists want to correct me on any of that before we move on. Skip?

DR. NELSON: A number of years ago, we held Pediatric Ethics Subcommittee meeting talking about HIV trials and they concluded, you know, you got to go where the disease is. So, it really wasn't an issue there. If you are willing to conduct the same trial in a developed setting, I mean, that's really the standard. And a couple of quick comment without belaboring the issue of the placebo group. I think it's quite complex, but I think the bottom line is the individuals within the area within which those trials are being done have to make, sort of, decision from a policy perspective about what's appropriate and what's inappropriate. And sometimes that may be for a low dose ACT type trial and sometimes that may not

be, such as this effective trial proposal in Latin America that fortunately was never conducted about 15 years ago. One of my favorite examples where I think a local -- and I think this goes to DSMB and gets back to this topic was a clinical trial of meningococcal vaccine conducted in the Gambia where they made an interesting policy decision that they would not distribute the vaccine unless it -- it was actually pneumococcal, not meningococcal. They made a decision that they wouldn't put it into general distribution unless it prevented pneumonia as opposed to meningitis. And so the DSMB actually made a decision to not even look at the meningitis data until they had reached a point where they can make an evaluation of pneumococcal end point, even though earlier on it did show that it was already approved in the US and in Europe for prevention of meningococcal -- prevention of meningitis. And I think -- and if you're interested, I'll send you the chapter that I wrote on this issue and -- but I think that was a legitimate ethical decision as a policy

perspective made by individuals in the Gambia. And so, an interesting question would be, in my mind, it's not so much about non-inferiority margin, but if you do this RCT I'm assuming it's going to be a DSMB looking at deaths in one arm, blinded, deaths in the other arm, blinded. And the decision about how many deaths would be appropriate in terms of imbalance between those two arms I think would have to be made in the setting within which that technology would ultimately be distributed. I mean, in other words ...

DR. FLEMING: Sure, you bet. This would fit within the normal construct of data monitoring committees monitoring a mortality end point with monitoring boundaries that are in place for both superiority and in this case futility would be a -- would be inferiority. So, yes, not a problem.

DR. NELSON: That's how you would do that.

DR. SIBERRY: Because in some ways, right, one percent lower efficacy with the ability

to reach tens of thousands of more people, because a product was more available, would go into some of what -- you decide about what was right for that setting, so it would have to be contextual. I fear that -- are we at the end of our time?

DR. FRANKA: Can I have just quick comment?

DR. SIBERRY: Yes, please. Brief, please.

DR. FRANKA: I will be brief. You know, what we discussed, these randomized clinical trials, sounds wonderful in ideal world. But in practicality, it is really difficult in those developing countries to have truly confirmed rabies exposure. You cannot -- how you will be measuring that there was virus in saliva? So, that's the first point. It will be almost impossible to do in most places around the world. Second, I would recommend to really consider alterative end points to death as an outcome and related to it, that probably FDA and community should be considering animal rule implementation

in those cases because I don't think those clinical trials will be feasible if they are done in developing world. Thank you.

DR. SIBERRY: Thanks for those comments. And you know, I would assume in a big trial like that, you would be collecting along the way information not just about rabies confirmation and the exposure, but also serologic results the DSMB could look at along the way because you could potentially learn something before you reach the end of that trial that would enable you to ...

DR. FRANKA: Majority of exposures are from street dogs who nobody ever see after they come to clinic, so I don't know how practically it could be.

DR. SIBERRY: The other thing I would say is we've had tremendous success with HIV clinical research in settings in Africa that are some of the resource poor settings. And so there's actually been huge development of infrastructure and capacity for fairly a high level research and in the settings that we also have represented

here. So, while it would take some careful work to make sure that those settings were prepared and have the capacity, I do not see that as the major barrier to getting it done. And with that, I'll turn it over to my ...

DR. FRANKA: You know, just PEP funding and rabies funding are different.

DR. SIBERRY: Money helps, but again capacity built is capacity that's there. And so, I think it sometimes takes little less money to add on to existing capacity then it does to developed to (Inaudible).

DR. BIRNKRANT: I think we've reached the end of our meeting and it was a very exiting meeting and I have a few closing comments on behalf of my colleagues of the FDA. I want to extend my sincere appreciation to all of those who participated in this rabies workshop. As we said in the beginning, we held this workshop not as a regulatory meeting for a specific product, but rather to begin the conversation and facilitate the discussion in the complex area post-exposure

prophylaxis for rabies. All of us recognize the need for accessible global rabies PEP regimens to address the numbers of deaths that are estimated to occur each year, more than twice from the recent devastating Ebola outbreak based on the literature and higher based on Dr. Wilde's analyses. We also recognize that current PEP with wound cleansing, vaccine, and RIG is highly effective at preventing lethal disease. Novel products to replace the RIG component that is intended to cover the first few days before meaningful vaccine response are challenging to develop as we've discussed at length. Today we heard about the global perspective from various presenters, the use of animal models and serologic assays and rabies product development and regulatory and ethical perspectives. We recognize that individual outcomes reflect the combination of factors. We further recognize that it would be important to have a very high level of assurance regarding the safety and activity of a new product to replace RIG before investigational

administration for study and suspected rabies exposure incidents because of the potential consequences of a less active product that are just not acceptable. We've had a good and rigorous discussion today on clinical trial designs and the ethics of clinical trials. Thank you, again, to the panel and speakers for helping identify research (Inaudible), which was part of the objective of this meeting and providing information as we move forward with the goal of developing safe and effective rabies products as components of rabies post-exposure prophylaxis. We look forward to future opportunities to meet again to discuss this important topic. Thank you very much.

CERTIFICATE OF NOTARY PUBLIC

I, SAMUEL HONIG, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

SAMUEL HONIG
Notary Public in and for the
State of Maryland

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I, EMMA KADEY, do hereby certify that this transcript was prepared from audio to the best of my ability.

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07/31/2017 _____

DATE EMMA KADEY