FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Thursday, April 25, 2019

8:30 a.m. to 4:36 p.m.

Tommy Douglas Conference Center

1000 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: Good morning. I'd like to call this meeting to order. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I would also like to identify the FDA press contact, Allison Hunt. If you are present, please stand. Allison will be joining us later.

My name is Dr. Lindsey Baden. I'm the chairperson of the Antimicrobial Drugs Advisory Committee, and I will be chairing this meeting. I will now call this meeting to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA to the far left.

DR. FARLEY: Good morning. John Farley, deputy director of the Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Good morning. Debbie

Birnkrant, director of Division of Antiviral Products, FDA.

DR. MURRAY: Jeff Murray, deputy, Division of Antiviral Products, FDA.

DR. TROY: Stephanie Troy, clinical reviewer, Division of Antiviral Products, FDA.

DR. BELL: Tanvir Bell, medical officer, Division of Antiviral Products, FDA.

DR. DEMING: Damon Deming, virology reviewer, Division of Antiviral Products, FDA.

DR. SWAMINATHAN: Sankar Swaminathan, University of Utah.

DR. SIBERRY: Good morning. George Siberry, medical officer, USAID.

DR. GRIPSHOVER: Barb Gripshover, infectious disease, Case Western Reserve University.

DR. GREEN: Michael Green, pediatric infectious disease, Children's Hospital Pittsburgh and the University of Pittsburgh School of Medicine.

DR. WEINA: Good morning. Peter Weina, infectious disease physician with the Office of the

Undersecretary of Defense.

DR. HOTAKI: Lauren Hotaki, designated federal officer.

DR. BADEN: Lindsey Baden, infectious diseases, Brigham and Women's Hospital, Dana-Farber Cancer Institute, and Harvard Medical School in Boston.

DR. CLARK: Nina Clark, infectious diseases, Loyola University Medical Center, Maywood, Illinois.

DR. FOLLMANN: Dean Follmann, biostatistics, National Institute of Allergy and Infectious Diseases.

DR. OFOTOKUN: Igho Ofotokun, Emory University in Atlanta, adult infectious diseases.

CAPT BURGESS: Tim Burgess, adult infectious diseases, Uniformed Services University and DoD's infectious disease clinical research program.

DR. PORTER: Laura Porter, patient representative.

DR. BAKER: Judith Baker, public health director, Center for Inherited Blood Disorders in

Orange, California and UCLA School of Medicine. I'm here today as the consumer representative.

DR. HARRIST: Ally Harrist, state health officer, Wyoming Department of Health.

DR. ELLISON: James Ellison, microbiologist, Division of High-Consequence Pathogens and Pathology, CDC Atlanta.

DR. MOORE: Susan Moore, director of the Rabies Laboratory at Kansas State University.

DR. BROWN: Catherine Brown, state epidemiologist, Massachusetts Department of Public Health and chair of the Compendium of Animal Rabies Prevention and Control, National Association of State Public Health Veterinarians.

DR. KARTSONIS: Nick Kartsonis, infectious disease and vaccines, Merck Research Labs, and today I'm serving as the industry representative.

DR. BADEN: I thank all of you for taking the time to join us and to participate in this discussion about this important question.

For topics such as those being discussed at today's meeting, there are often a variety of

opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Dr. Hotaki, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug Administration is convening today's meeting of the Antimicrobial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special

government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of one or more possible pathways for approval of rabies virus

monoclonal antibodies for use as the passive-immunization component of post-exposure prophylaxis.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Nicholas Kartsonis is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Kartsonis' role at this meeting is to represent industry in general and not any particular company. Dr. Kartsonis is employed by Merck Research Laboratories, Merck & Co.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have had regarding the topic at issue that could be affected by the committee's discussions. Thank you.

DR. BADEN: Thank you.

We will now proceed with the FDA's introductory remark from Dr. Murray.

FDA Opening Remarks - Jeffrey Murray

DR. MURRAY: Good morning. I'd like to welcome and thank all the committee members and consultants attending today's meeting. As you know, today's topic is the development of rabies monoclonal antibodies as a part of rabies post-exposure prophylaxis or PEP. As you'll hear,

there are three components to rabies PEP for significant, that's category 3, exposures. That's wound washing, vaccine, and rabies immunoglobulin or RIG, and today we are addressing monoclonal antibody cocktails as a substitute for the RIG polyclonal versions, which is the passive immunity component of PEP.

Rabies is a fascinating topic for multiple reasons, such as the many animal vectors, the international issues associated with it, and the often weird and tragic stories by which people get exposed. But rabies is also fascinating because of how ferocious of an infection it is. In fact, it's the most lethal of all infections and rarely leaves a survivor once symptoms develop. Death occurs in a matter of days or weeks.

The nearly 100 percent mortality rate with clinical rabies infection is the bad news. The good news is we have tools to prevent it. In fact, rabies PEP approaches 100 percent effectiveness when properly and promptly administered. Given this severity of rabies infection, it's important

when developing a replacement component of PEP that we have great assurance in its likely efficacy, even before we start clinical studies in rabies-exposed individuals for obvious reasons.

Therefore, even more so than for other types of therapeutics, I believe for rabies monoclonal antibodies, we need to rely heavily on data and information from early phases of drug development, including nonclinical data such as cell culture, animal data, and other early clinical data; rabies virus neutralizing antibodies for example. We need to rely on this in order to proceed with further development in rabies-exposed people.

Today, you will hear FDA-sponsored presentations that provide all the necessary background on rabies pathogenesis, rabies PEP, and the challenges and development of the passive-immunotherapy component of PEP. You'll also hear a summary of the outcome of a workshop held in 2017 on this topic. And importantly you will hear that although it is possible to conduct clinical trials in rabies-exposed individuals, it

is not feasible to design trials that definitively establish the efficacy of monoclonal antibody cocktails for the endpoint of survival.

This is the crux of the matter for today's meeting. We will be presenting proposals for rabies monoclonal antibody development, both for commencing trials in rabies-exposed individuals and also for supporting a convincing application for marketing. We are not proposing a new regulatory mechanism. We envisioned the approval mechanism as a traditional approval based on clinical endpoint data, but one that is also highly fortified by other data, including cell culture data, animal models, and serologic comparisons in healthy volunteers.

We think this approach is similar historically to what has been used for polyclonal RIG and other passive immunoglobulin therapy, so we're seeking concurrence from the committee on this general approach, and we're also asking you to opine on some quantitative parameters or guardrails for the amount and types of data that would provide

the most convincing package, both pre- and post-approval.

With that brief introduction, I'd like to have us proceed with the presentations. The first presentation will be Dr. Tanvir Bell, who will be providing the background on rabies and why monoclonal antibodies are being developed for rabies PEP.

DR. BADEN: Thank you.

Dr. Bell?

FDA Presentation - Tanvir Bell

DR. BELL: Good morning. Can you hear me okay? It's kind of weird having the microphones on two ends here.

My topic of discussion today is a background on rabies and to discuss why monoclonal antibodies are being developed for rabies post-exposure prophylaxis. The outline of my talk, or the content, includes, to describe the recommendations for and components of rabies post-exposure prophylaxis, or PEP; to describe characteristics of rabies pathogenesis; to discuss the advantages and

disadvantages of monoclonal antibodies for use in place of rabies immunoglobulin, or RIG, as part of rabies PEP.

As Dr. Murray brought up, we did have a 2017 public workshop on this topic and the challenges and nuances for monoclonal antibodies as rabies PEP was discussed there, and we're fortunate that some people at the table were participants and experts that contributed to that public workshop.

As Dr. Murray said, rabies is a serious condition. A clinical disease develops in almost all patients, in almost 100 percent, and it's fatal. There are many deaths, about 60,000 deaths per year worldwide. Post-exposure prophylaxis luckily is very effective, about 100 percent. It's widely used, so 23,000 people per year in the United States and 17 million people per year globally. Most rabies deaths are due to no PEP or incorrect PEP.

In the United States, we may worry about bats, raccoons, or foxes causing rabies, and this part of the map from the WHO illustrates the global

deaths from rabies. The areas in gray are areas that are free from canine rabies, and in the United States, we're fortunate not to have many deaths annually from rabies. However, the rest of the world is not so fortunate and have many more deaths; in some areas of the world, over 8100 deaths per year. And you can appreciate on this map that less a geographic area is free from canine rabies and southeast Asia and Africa has a significant burden of death from rabies.

As Dr. Murray mentioned, there are three components for rabies, post-exposure prophylaxis: extensive wound cleansing, rabies immunoglobulin, and rabies vaccine. Some guidelines have differences in who should get RIG or rabies PEP at all. The ACIP, the Advisory Committee on Immunization Practices, suggests that we provide rabies PEP based on animal types.

So if you have exposure to a skunk, raccoon, bat, or fox in the United States, folks should get rabies post-exposure prophylaxis regardless of rabies testing of the animal. For dogs or cats,

however, they can be watched, and rabies PEP, including RIG, does not necessarily need to be given unless we know that the dog is rabid, dog, cat, or ferret.

The WHO quantifies who should get RIG or rabies PEP based on the category of exposure. Category 2 is a nibbling of uncovered skin, minor scratches, or abrasions without bleeding. In this situation, PEP should be given without RIG, so the vaccine and then washing.

Category 3 exposures, however, when they're single or multiple transdermal bites or scratches, licks on broken skin, or contamination of mucous membranes with saliva, or contact with bats, the full rabies PEP should be given with rabies immunoglobulin, and the regimen should be given as soon as possible, which is a realistic concern in terms of availability of products to use for rabies PEP.

This table shows the differences between a ACIP and WHO category 3 exposures in regards to rabies PEP. On day zero, when someone is exposed

or bitten, extensive wound cleansing should be done, and also on day zero, if deemed necessary, RIG should be provided. In the United States, the form of RIG that is commonly used and the only type of RIG recommended is HRIG, or human rabies immunoglobulin. The rest of the world, at day zero, people that need RIG can get the form of RIG of HRIG or equine RIG rabies immunoglobulin generated by horses at day zero.

The rabies vaccination is a vaccination series. For the ACIP, they recommend 4 doses IM, and the WHO has different recommendations. One of the options is 4 doses IM for saving of resources. There also is an intradermal option and multiple site injections at different types to decrease the amount of days you have to give RIG.

It's important to give RIG as much as is anatomically feasible in the area that's involved. And also, if someone received rabies vaccination in the past, they don't need RIG, but they would get some therapy as part of post exposure prophylaxis.

This is, again, those three components of

rabies post-exposure prophylaxis in the same order that Dr. Murray said, so thorough wound washing, prompt initiation of a vaccine series, and rabies immunoglobulin in and around the wound. These first two components, there are estimates that they're effective in almost 99 percent of rabies virus exposures. As a result, if we were to design a noninferiority trial of rabies monoclonal antibody to HRIG, the sample size would be really, really large.

The best data we know about the benefit and utility of RIG is from a 1954 field trial in Iran. An incident occurred where a rabid wolf bit 29 individuals over a 5-hour period. Those 11 individuals, who did not have head bites, whether or not they got RIG, they all survived.

The 18 that had bites to the head and face all got the suggested wound washing and vaccine. The 13 that got RIG, there was only one death, whereas the 5 that didn't get RIG, there were 3 deaths, 60 percent. This shows the mortality benefit that RIG could provide.

The child on the top left-hand corner can really illustrate how RIG works. This child was bit down to meninges. He got RIG, wound washing, and the series, and actually survived, which is great.

This was a different time, 1954 versus 2019, and things given were different. Rabbit serum globulin was given and a sheep brain-derived vaccine was provided. This was also a unique situation in that we knew that the wolf was rabid. We don't always know the rabies status of the animal providing the exposure.

This picture depicts rabies pathogenesis after animal exposure. The bottom left is where the role of PEP would occur at the site of a bite from a rabid animal. Once the rabies comes from the animal saliva, it then has to go through the muscle to the nerve, then it traverses the nerve at a certain rate. And generally in weeks to months, as Dr. Murray pointed out, you will see symptoms of rabies with encephalitis and ultimately death. This is also the reason why head wounds are

particularly problematic, as the length from the bite to the head is shorter in that situation.

Now, I have to step forward again. This is a graph showing the contribution of passive immunization to post-exposure prophylaxis. There's a lot on this slide. It's a busy graphic, but I'd like to bring your attention to the right hand Y-axis of antibody response and the X-axis is time.

The time we're worried about is the time of this red arrow. When someone is given rabies vaccination series, it often takes 7 to 14 days for that antibody response to begin. The antibody response is generated and peaks, and then declines over time. The RIG or monoclonal antibody would provide protection in those first 0 to 7 days, and the benefit from RIG on this slide is shown by this highlighted yellow line.

The WHO uses 0.5 IUs per mL as the threshold to define vaccine effectiveness. There is no known threshold to define HRIG or monoclonal antibody effectiveness in those early time points. Stephanie will talk more about serologic correlates

of rabies infection.

This slide shows how RIG is generated. On your left-hand side, individuals or volunteers would be hyper-vaccinated with multiple doses of rabies vaccine. Their serum would then be collected and plasma generated.

There are two types of RIGs, HRIG and ERIG, as we discussed. HRIG, the first two HRIGs that were approved in the United States were approved over two decades ago, and the basis of approval included reference to the field trial and in Iran previously described, and also the fact that these human RIGs were safer than ERIG at the time.

KEDRAB is a form of HRIG that was approved recently in 2017, and the basis of the approval was serologic correlates of disease in 150 healthy volunteers but also had the benefit of postmarketing information of 250,000 patients in areas of the world where this product was already approved prior to the application to the United States.

There are limitations to rabies

immunoglobulin, the high cost, which leads to less than 2 percent utilization worldwide of rabies immunoglobulin. There is the issue of cold storage. Potential shortages can occur, and there have been potential shortages in the United States. There also is the potential for bloodborne pathogens, but to our knowledge, there hasn't been bloodborne pathogen transmission by rabies immunoglobulin. And indeed, virus inactivation steps are required.

What we're thinking about is rabies monoclonal antibody cocktails for use for passive protection in rabies. The WHO suggests that greater than 2 monoclonal antibodies that target non-overlapping antigenic sites for the rabies virus outer G protein be used as part of a cocktail.

This schematic on the top left is the rabies bullet-shaped virus with the spikes coming out of the surface, which are the G proteins. I'd use the pointer, but I don't want to run back and forth anymore.

There are potential advantages and potential challenges to rabies monoclonal antibody cocktails. The potential advantages are increased consistency, more rapid production capability, and no bloodborne pathogen transmission risk. There are potential challenges. It's a narrower spectrum of rabies virus coverage, perhaps 2 monoclonals versus many monoclonals, and also there is the potential for greater vaccine interference in those later time points.

A package that would come to the FDA for consideration for approval would include some of these three buckets of information here, nonclinical data for which Dr. Deming and Dr. Ellison are going to speak more about in the next two talks.

This data would provide neutralizing activity versus diverse rabies virus strains and also proof of concept, selection of monoclonal antibody dose for initial clinical and evaluations. The way we can evaluate efficacy to some degree is by serologic assays where we could see the passive

protection during those first few days and also effects on the rabies vaccine response at later time points.

For clinical trials, Stephanie will talk more about clinical trials after the break. We'd want to do clinical trials in non-rabies exposed populations, so that would be like healthy volunteers, and from that population, we'd want to see safety of the product and also serologic endpoints. These components, up to the non-rabies exposed population, is what we're asking the advisory committee to suggest and comment on, on the first two questions that we will be asking you.

After we've got this aggregate of information, we'd want to move to suspected rabies-exposed population before a drug got approved in the United States. In the suspected rabies-exposed population, we would get information about safety, serology, and also mortality information.

As discussed, we had a 2017 public workshop on rabies post-exposure prophylaxis in the use of

monoclonal antibodies for post-exposure prophylaxis. This was a public workshop to facilitate sharing of the available data and complexities in the field of rabies PEP. It was a forum of discussion for identifying research gaps relevant to regulatory and public health issues.

The objective was to discuss challenges and identify additional scientific work needed to advance this area and field. Additional information provided by people at the public workshop and the discussion that perhaps is not fully covered today includes perspectives from WHO, industry, and experiences from physicians and trialists at rabies treatment centers. We also discussed ethical considerations in rabies monoclonal antibody trial designs.

The picture on the right is a graphic of the stakeholders at our 2017 public workshop. Some take-away points included that the hamster model is most established, and Dr. Ellison, who was at the public workshop, discussed that, and he will be discussing aspects of animal models in the next few

talks.

We also learned about the limitations of rabies virus neutralizing antibody, RVNAs, tests as a surrogate for efficacy, and that the correlation of RVNAs from passively-administered RIG with mortality is unknown. Susan Moore certainly has expertise in that field, and she's at the table.

We heard the need expressed by WHO and providers that monoclonal antibodies would be of benefit. There are some logistic issues with administration of RIG or a new monoclonal antibody and for trials issues, including the fact that wound injection may be difficult in different areas, that someone might get bitten by rabies such as the face or close to the eye.

Also, we don't always know that the animal is rabid. We don't always have confirmation of the status. In fact, the amount of information we've gotten -- areas that are rabies treatment centers have decreased in knowing how many animals that affect individuals are rabid.

There is a monoclonal antibody that's

approved in India in 2016, but this is only one monoclonal antibody that has probably the best activity against dogs. For the company to approve this in India, the pivotal trial took 2 years to enroll 200 patients, which illustrates some problematic logistics that might happen in a trial to evaluate rabies monoclonal antibodies in place of RIG.

Also, we discussed if RIG-controlled trials or placebo-controlled are needed. In general, the thought was that placebo-controlled trials are probably unethical. Dr. Siberry was a moderator for that discussion, that part of our public workshop where we discussed that.

I'll end with our acknowledgement slides. At the FDA, we're fortunate to have a multidisciplinary team, which is definitely needed in areas such as this. Jeff Murray, our deputy, has provided a lot of leadership, and Sarah Connelly in the back of the room was very instrumental in our public workshop and has provided guidance throughout the process of

preparing this advisory committee talk and workshop.

We're fortunate to have the input from pharmacologists/toxicologists. Chris Ellis specifically gave a lot of assistance to us. We have a wonderful statistics group in the Office of Biostatistics. Hengrui Sun provided a lot of support. We also have the benefit of having clinical pharmacologists in the Office of Clinical Pharmacology, and Mario Sampson from that office provided a lot of assistance.

Immunoglobulins are regulated by the Center for Biologics Evaluation and Research, and we were very fortunate throughout the public workshop and for this advisory committee to work with leaders in the field, including Robin Levis, who's in the audience, and Dorothy Scott. We'd also like to thank the experts from the 2017 rabies workshop. And with that, I'll end my talk and turn it over to Dr. Deming.

DR. BADEN: Thank you, Dr. Bell, and Dr. Deming, please take the podium. To the

committee, we will do clarifying questions after all of the speakers have spoken. So please save your questions, and we will get to them after all the speakers have spoken.

Dr. Deming?

FDA Presentation - Damon Deming

DR. DEMING: Good morning. I'm going to discuss cell culture neutralization assays and the role that they play and might be expanded to play, in the development of antibodies for rabies post-exposure prophylaxis.

I'll begin by going into a little more detail or into one of the potential challenges commented on by Dr. Bell, which is that monoclonal antibodies might be expected to have a narrower breadth of coverage versus antigenically diverse rabies virus strains. Then I'll give a brief description as to how these neutralization assays work, and wrap up with an example of how the results from those assays might be used to allow for direct comparisons between an experimental product and an approved polyclonal RIG product.

Ideally, any monoclonal antibody replacement to RIG would be able to neutralize any circulating virus at least as well as a polyclonal product. But that actually is a challenging goal; it might be a challenging goal to achieve.

The ancestor to contemporary rabies was believed to have spilled over from a bat host some 900 to 1500 years ago, and since that time it's jumped into several other hosts, and adapting as it goes along. Over time and as it adapts to new hosts, it accumulates several changes across its genome, including against the glycoprotein, which as Dr. Bell mentioned is the only extracellular protein and is the target for all neutralizing antibodies.

What I'm showing here is just a published phylogenetic tree, and this just shows the relationship between various virus strains, a couple thousand included in this analysis, based on similarity between the amino acid sequences of the glycoproteins. Just looking at it as a whole, you see there's a lot of diversity across the spectrum

of potentially circulating rabies virus strains. In general, any given glycoprotein is going to be most closely related to the glycoproteins of isolates pulled from the same host species in the same geographic region, and presumably around the same time, as you might expect.

This is a cartoon of the rabies virus glycoprotein. In the extracellular domain, there are several known antigenic sites, and these tend to be targeted by neutralizing antibodies. I believe the prevalent ones are antigenic sites 2 and 3 for most human response or most natural responses to the protein.

These antigenic sites include conformational epitopes like 2 and linear epitopes like 3. As Dr. Bell mentioned, the WHO recommends that any monoclonal antibody cocktail consists of at least 2 monoclonal antibodies targeting different epitopes and of course a polyclonal RIG, which is pooled from hyperimmune serum from several different donors, just like they target far more epitopes than that.

The rationale for including multiple antibodies targeting different epitopes is that it's not unlikely that a given circulating strain is going to contain polymorphisms within an epitope that could impact the binding and neutralization of an antibody in this example 1.

Ideally you would have at least one active antibody in any cocktail. Of course, some viruses will contain polymorphisms in more than one site. One concern is that you're more likely to lose the activity of a product as a whole when you're looking at a monoclonal antibody cocktail as opposed to a polyclonal RIG.

How might we actually go about assessing this potential risk? That's where we're going to rely on the neutralization assay. And these are used now for measuring rabies virus neutralizing activity in samples, whether from a monoclonal antibody prep or from hyperimmune serum. Several of these assays are already validated for use as clinical and veterinary purposes, and these include the Rapid Fluorescent Focus Inhibition Test, or

RFFIT, and the Fluorescent Antibody Virus Neutralization Test. They're often, as I mentioned, used to evaluate responses to vaccination in people and animals.

They're also used to assure comparable potency in RIG production and make sure that you bottle comparable amounts. More relevant for our discussion, they can be used to compare the neutralizing activity and the breadth of that activity between different products.

Hopefully the people who actually run these assays will forgive me. This is a very simplified example of how these new neutralizing assays might be done, but I was just trying to illustrate a couple of basic principles.

Imagine that this square with circles is a multi-well tissue culture plate, and each circle is a well that contains a monolayer of cells highly susceptible to infection by rabies virus. Now eventually every well is going to be exposed to the same amount of virus, 50 TCID50, in this example. But before that occurs, it's going to be mixed with

one of several dilutions of an antibody.

Ultimately what's going to happen here is that we're going to be testing each dilution of antibody's ability to prevent infection, and each concentration is going to be tested and replicated 6 times in this example. After a certain amount of time, you look for evidence of viral replication, and the wells where virus replication is detected are shown in green -- hopefully it's green -- on this slide.

The endpoint for this assay is the concentration that prevents infection in 50 percent of the wells, so the 1 to 32 dilution in this example. Using this information, we should be able to calculate the amount of neutralizing antibody associated with that dilution. That endpoint is often referred to as a 50 percent effective concentration, or EC50 value, and that's the term I'll be using.

Now, there are two different units that that value can be reported in. Generally, when you starting concentration of the neutralizing antibody

is known, it's going to be reported in terms of grams per milliliter or micrograms per milliliter. If it's something more complex like from human or animal serum, where the amount of neutralizing antibody isn't known or is mixed with several other antibodies, many of which won't even bind to rabies virus, it's going to be expressed in terms of international units per milliliter or IU per mL.

In the first case, determining the EC50 value is pretty straight forward, the starting concentration, showing 1 microgram per mL in this example, and the endpoint dilution 1 to 32. So it's just simple math to determine that the EC50 value is 31 nanograms per mL. In the second case, such as if this were hyperimmune serum, you need to rely upon an assay run in parallel, except that's going to use a reference antibody with a known EC50 value.

In this example, the reference neutralized 50 percent of the wells at a 4-fold lower dilution, meaning that it was 4-fold more potent. If the referenced antibody has an EC50 value of 2 IU per

mL, it's simple to calculate that the EC50 value for the sample is actually 0.5 IUs per ML.

How can we actually use this information now to predict neutralization potential in vivo? Any such analysis like that is going to require knowledge of the concentration at the most relevant site. As Dr. Tanvir mentioned, this is going to be within the tissue of the bite wound.

Now, it's difficult to measure concentrations in tissue, so what I'm doing for the subsequent analysis is actually using the concentration of the drug as administered, as it's inoculated into the site to estimate the concentration in the tissue; the idea being that any dilution that occurs between the time that the solution leaves the syringe to the time it interacts with the virus in the tissue is going to be consistent between any immunoglobulin-based product.

Then the estimate is then done simply by looking at the ratio of the concentration of the antibody -- I put mAb there; it should be

antibody -- over the known EC50 plotted. This is just one of many ways to actually do such an analysis. In this hypothetical example, I'm showing a neutralization profile of a polyclonal RIG, and the administered concentration is 150 IUs per mL.

On the Y-axis, we're looking at all the strains that were tested. We have a couple of common laboratory strains on the left; 10 terrestrial isolates in the middle, and this includes viruses taken from things like dogs and skunks; and 10 bat isolates on the right. On the Y-axis, I'm simply reporting the data as I described before. It's the ratio of the antibody concentration over its EC50 value as determined on the neutralization assay against that strain.

In this example, 22 neutralization assays were run. These values tend to be large, so I log transform it just to make it easier to see. For example, in this case, this RIG product has a value of about 10,000 against CVS-11, meaning that at that concentration, 150 IUs per mL, that's about

10,000-fold above the CC50 value. So we predict that it has a pretty high neutralization potential against that isolate.

The black dotted line, or any value falling on the black dotted line, means that the concentration being administered and EC50 value are equal, so that wouldn't be very reassuring. Any value assigned to the red dashed line means that no EC50 value was tested or was achieved even at the highest tested concentration, which for this example I'm assuming is going to at least be equal to the administered concentration.

Taking a step back, looking at these results, we might interpret these assays as indicating that RIG has activity against all of the tested isolates, although there is some variability between the least susceptible and most susceptible strains, about an 80-fold difference in this example.

Here is a neutralization profile of a hypothetical monoclonal antibody that's going to be delivered at a concentration of 2.5 mgs per mL, so

it's pretty high. Against many of the strains, it appears to have a higher neutralization potential than HRIG. Against a few others, it's about comparable to a HRIG, and against a handful of isolates, it was actually less than. In the case of the last one, the isolate taken from a tricolored bat, it doesn't appear to have any neutralizing activity at all.

Now, when combining monoclonal antibodies to form a cocktail, ideally your second and/or third monoclonal antibodies would cover any potential gaps from the first one. I've just overlaid the profile of the second monoclonal antibody. In this example, there were some mixed success. In some cases, the second monoclonal antibody appears to cover potential gaps from the first one, such as is in the case of the mongoose from Puerto Rico, but there were also a couple of examples where it did not match the activity of HRIG, and that's a concern where the first one was also not particularly potent, such as in the case of the eastern red bat isolate. These indicate potential

gaps in coverage, which we would find concerning.

Finally, this is just the neutralization profile for the combination of 2 monoclonal antibodies. These have been mixed in a 1 to 1 ratio by mass. And as you might expect, the neutralization profile is about equivalent to what you expect from more potent of the two component monoclonal antibodies.

Overall, if we were to analyze a data set that looked like this, we might conclude that it would be expected to neutralize at least as well as RIG against many isolates, although its breadth of coverage is narrower and there might be some gaps.

It's also worth pointing out that we don't know what the biological or clinical cutoff values might be. For instance, we can't say that any monoclonal antibody cocktail that doesn't achieve a value of 2 or higher is going to fail as PEP. We don't have enough information to draw those conclusions, although hopefully other models such as the challenge models that Dr. Ellison will be describing can be used to provide some of

that -- or at least provide some insight into those types of relationships.

Just to summarize the key elements of this short presentation, neutralization assays can be used and are used to evaluate the breadth of neutralizing activity of monoclonal antibodies antigenically diverse strains. They can also be used to make comparisons between the activity and breadth between various products.

Now ideally, any such assay like this would be standardized and available to sponsors, and such a standardized assay would hopefully include several rabies virus strains reflecting the antigenic diversity of circulating strains with consideration given to viruses that would most likely be involved in human exposures. It would also incorporate strains with polymorphisms at sites known to affect the neutralization of the individual monoclonal antibodies for any cocktail.

It's yet to be determined how best to interpret these data, and that's a discussion that's going to need to be ongoing. For example,

how much lower than an approved RIG product against a certain strain could a cocktail fall and still be considered to be adequate?

That's it. I will refer you to Dr. Tanvir's nice acknowledgement slide. It's the same group. Thank you.

DR. BADEN: Dr. Troy?

DR. ELLISON: Yes. Thank you.

DR. BADEN: I'm sorry. Dr. Ellison is next.

DR. BADEN: Thank you, Dr. Deming.

Dr. Ellison?

Speaker Presentation - Dr. Ellison

DR. ELLISON: I'd like to thank you guys for having me back here to give a brief review of the talk I gave at the workshop in 2017. I'm going to talk about the use of rabies models in animal product development.

Studies of rabies pathogenesis began a long time ago, over 200 years ago, and it started when investigators basically swab the mouth of a rabid dog, lacerated another one, and introduced that infectious saliva into that animal experimentally,

thus experimentally passing rabies.

Pasteur really built on that in the early 1800s and demonstrated that it could be transmitted from animal to animal using the rabbit model, and what this did was it really set a foundation for future studies in pathogenesis diagnosis and eventually vaccine production.

Rabies is a disease of antiquity. It's a disease of animals, and it's probably one of the most thoroughly researched. Different models have been used from the 1800s, starting with dogs and rabbits, that evaluated different serum treatments, and the use of rodents, such as mice, for evaluating different nerve tissue vaccines. Guinea pigs were also investigated.

In the '50s is when early studies in pathogenesis of hamsters began, followed by veterinary vaccines using foxes and other wildlife reservoirs, and then eventually to nonhuman primates for the current human diploid cell and other vaccines. Really, most of what we know about the events that take place during rabies infection

has been learned from experimental animal models.

As we saw earlier today, the rabies virus is pretty small. It's about 12 kilobases and has 5 proteins. Only one of them is on the exterior, and that's the glycoprotein. It's the most critical for pathogenesis. It's also one of the most diverse. It's responsible for receptor binding and fusion, and it's where the site of most antibodies are directed, 4 epitopes and 2 minor sites.

Even within a species, there's multiple variants that are transmitted. On the phylogenetic tree here, you can see the diversity of rabies virus variants based on the full glycoprotein protein structure, and even within some species, there's multiple variants transmitted. For instance, the common big brown bat maintains at least 4, depending on what geographic location it's from.

Rabies virus transmission is pretty simple as was outlined this morning. It's the same process in humans as animals. Without exception, the virus is introduced from the infectious saliva

of a rabid animal into a susceptible host, typically by bite. The only human-to-human transmission is occurred through solid organ transplantation.

After the bite, there may or may not be replication at the local site, but it rides along the actin filaments to the nerve, where it gets into the nerve tract, to the spinal cord, to the brain, where it replicates and then travels towards the exit portals; most importantly, the salivary glands where it can be introduced into the next susceptible host, thus maintaining a transmission cycle. And here at this synaptic cleft in the neuromuscular junctions, what we hypothesize is the most important place that the passive immunization is going to be effective at blocking the virus before it can spread down the neuron.

WHO recommends, in addition to in vitro testing, RIG and other products to determine neutralizing potential should be evaluated in vivo. Reproducible animal models should be used for assessing the effectiveness of any medical product

for use at the site of exposure. The in vivo half lives of antibody preparations for passive immunization and the duration should be determined, especially for humanized monoclonal antibodies or monoclonal antibodies intended for human treatment.

In using animal models for rabies post-exposure prophylaxis based on pathogenesis studies of experimental rabies, we're able to reproduce incubation period, clinical signs of disease, and one of the most critical components is the failure of vaccine alone to prevent disease for the majority of isolates. If you're able to prevent disease a hundred percent of the time just using vaccine, your studies using the passive component really don't say much.

At CDC, we're always working to develop better models, and recently we've developed a bioluminescent mouse model to evaluate rabies pathogenesis. This is used using a recombinant rabies virus expressing a fluorochrome, and it allows for real-time visualization of rabies virus dissemination towards the central nervous

system.The animals do present clinical signs and that demonstrates the natural disease process. There are a few limitations. This model is extremely expensive and some of the features are not widely replicated.

What we use as our workhorse for evaluating different biologics is the hamster model, and it's been widely used as a standardized model to evaluate different post-exposure prophylaxis schedules. In early studies of post-exposure prophylaxis, or PEP, hamsters were found to be extremely sensitive to rabies virus challenge and demonstrated a more reproducible attack rate than other rodent models or nonhuman primate models.

The high attack rate observed after intramuscular injection of a large viral inoculum of rabies vaccine is unable to provide complete protection, thus facilitating the hamster model as a model of severe human exposure. The greatest utility of the hamster model is the ability to evaluate the passive component of antibody post-exposure prophylaxis.

When experimentally infected, mortality rates of hamsters treated with vaccine alone approach that of controls, which is about 80 to 100 percent mortality. When passive immunoglobulin is given in addition to vaccine, survival rates approach 70 to 100 percent, and what this does is demonstrate the effective contribution of passive immunoglobulin that's separate from rabies vaccine.

The efficacy of immune serum plus rabies vaccine in the hamster model is similar to that observed in the few human trials involving immune globulin that was talked about this morning, the trial in Iran. Given the added contribution of passive antibody was only demonstrated in the most severely exposed people, the people that had the head wounds and bites, and animal model to evaluate the component of PEP should be sufficiently rigorous that vaccine alone is unable to prevent disease.

There are some issues with experimental animal models. The reproducible challenge in using these -- we call them street isolates or primary

isolates derived from nature, there's not an indefinite stock, so these have to be adaptive to cell culture, and there are some changes that can occur when you adapt a virus to cell culture. These are RNA viruses.

We see variation in mortality by species and strain, outbred wild animals versus inbred laboratory-bred animals. It doesn't exactly replicate the prodrome associated with human disease versus disease with non-reservoir versus target animals. Basically, all mammals that have been sufficiently studied are susceptible to rabies virus. And as you saw earlier, each species maintains a unique variant associated with it.

There are issues associated with heterologous or homologous variants that are proposed to be influenced by the species barrier. For example, when using raccoon virus in raccoons, we can induce a hundred percent mortality. However, when we try to use a raccoon variant with the same dose in hamsters, we only have 30 percent mortality. There's also cost and ethical

considerations, use of companion animals such as dogs, and you saw the number that it would take to power these studies; yet I couldn't imagine having thousands of rhesus macaque nonhuman primates. That would be a lot.

In summary, a well-characterized animal model is essential to evaluate any proposed anti-rabies biologic for use in PEP. The global breadth of rabies virus variants must be considered when evaluating new animal models, and thus far the hamster model shows the greatest potential in addressing many of the confounding factors associated with other animal models when evaluating PEP.

Thank you for your time, and I refer it back to --

DR. BADEN: Thank you, Dr. Ellison.

We've completed the first round of discussions and presentations. We will take the break a little bit early and resume at what time? In 15 minutes?

We'll resume in 15 minutes. I will remind

members not to discuss any aspect of today's topic at the break. We'll resume at 9:45.

(Whereupon, at 9:27 a.m., a recess was taken.)

DR. BADEN: We shall resume. If Dr. Troy can take us through the next presentation, please?

FDA Presentation - Stephanie Troy

DR. TROY: Good morning. Tanvir already gave you a background on why monoclonal antibodies for rabies post-exposure prophylaxis are being developed, and you've heard about the nonclinical studies that can be done to evaluate rabies monoclonal antibodies. I'm going to be talking about the clinical trials and the data that could be obtained from those and also a proposed development pathway.

Specifically, I'm going to be talking about the strengths and the weaknesses of the surrogate endpoints and the logistic constraints with mortality endpoint. Then when we talk about a possible development pathway, it's going to be divided into information needed prior to clinical

trials in rabies virus-exposed subjects and information needed from clinical trials in rabies virus-exposed subjects.

From this point forward in the talk, whenever I talk about rabies virus-exposed subjects, I mean subjects with World Health Organization category 3 exposures where the rabies status of the biting animal is not known because in real-world practice, most of the time when people present for PEP, they don't know whether the animal was actually rabid or not.

When we're talking about data from clinical trials, we have to divide it into the trials in healthy subjects who have not been exposed to rabies and the trials in rabies-exposed subjects. And naturally, as mentioned before, we have to do the healthy subject trials first because the stakes are lower if we get it wrong.

In healthy subjects, we can get important data on safety, on pharmacokinetics, and most importantly half-life to make sure that the monoclonal antibody lasts long enough to cover that

window period before the vaccine response kicks in, and we get information on serologic endpoints, otherwise known as the rabies virus neutralizing antibodies, or RVNAs, when the monoclonal antibody cocktail is administered intramuscularly or possibly subcutaneously.

In the rabies virus-exposed subjects, we get more information on safety. We confirm the pharmacokinetics and the serologic endpoints when the monoclonal antibody cocktail is administered in and around the wound, and then we get information on rabies mortality. The three highlighted in red are the three endpoints that might be used to evaluate efficacy in clinical trials, and these are what I'll be talking about more in the next few slides.

When we're talking about serologic endpoints, we're talking about the assays that Damon described earlier for cell culture to measure the rabies virus neutralizing antibodies. Only in this situation, instead of doing serial dilutions of the monoclonal antibody cocktail itself, you'll

be doing serial dilutions of serum from the study subjects who received PEP.

In these study subjects, there are two sources for the RVNAs. In passive immunization, when the subjects received the monoclonal antibody cocktail, or the RIG, you have the antibodies. You inject them in and around the wound, and then those that make it into the serum are measured there as serum RVNAs.

With active immunization, meaning you would administer the inactivated rabies vaccine, you inject the inactivated rabies virus vaccine intramuscularly. You have this whole immune response, and one of the endpoints from the response is development of antibodies. And those that neutralize the specific rabies virus that's used in the assay are measured as serum RVNAs.

One important thing to note is that these assays do not distinguish between these two sources of RVNAs, but they're different, because if you think about it, with active immunization, when you measure the RVNAs from active immunization -- and

we talked earlier about a threshold of 0.5 international units per mL being protective -- that doesn't mean that that level of antibodies as protective. That means that that amount of antibodies is produced as part of a whole immune response that might also include cellular immunity is protective.

The other big difference is that with active immunization, you have the antibodies in the serum and then they travel to the tissue where they are used to neutralize the rabies virus. But with passive immunization, you're injecting the antibodies directly where they're needed into the tissue, and then you measure those that make it into the serum, and rabies virus does not establish viremia in the blood, so this is an indirect measure of the levels in the tissue where it's needed.

The third thing to point out is that only one rabies virus strain is used in these assays, typically the CVS-11 strain. These assays don't measure breadth of activity against the diversity

of rabies strains; they measure the neutralizing activity against one strain.

Now, when we're talking about serologic measures, there's two distinct time points that are important. I'll show that on this figure, where on the Y-axis RVNA, and it's a logarithmic scale, and the X-axis is the days after PEP initiation. The black line is subjects who received vaccine alone. This is a hypothetical example. I made up these numbers. The red dotted line is HRIG alone. The red solid line is subjects who received HRIG plus vaccine. The blue dotted line is the mAb cocktail alone, and the blue solid line is subjects who received the mAb cocktail plus vaccine.

Now, at early time points up to day 7, all of the RVNA that is measured, or almost all of the RVNA, is from the passive immunization with the monoclonal antibody cocktail or RIG. You can see here on the black line that the subjects who received vaccine alone don't have any detectable RVNA at these time points, and you can also see that the subjects who received the monoclonal

antibody alone have the same amount of RVNAs as those who received the monoclonal antibody plus the vaccine.

Now, as measured before, there's no established protective threshold. With HRIG, the levels typically only reach about 0.2 to 0.3 international units per mL, but we know that these are effective. This is an indirect measure because it's measured in serum, not tissue.

Later time points from day 14 on are a measure of vaccine interference, not of the efficacy of the mAb or the RIG product. You can see here that the highest levels in the black line are from recipients who received vaccine alone, and if you think about it, this makes sense because even if you're administering the passive component at a different body site than the vaccination, when you administer the antibodies with the inactive rabies virus, there's going to be some neutralization that occurs that diminishes the vaccine response.

So there's usually some amount of vaccine

interference, but as long as the vaccine-induced RVNAs are above the 0.5 international units per mL threshold, then it's still considered protective.

I don't mean to indicate that this time point is not important because it is, because the last thing we want to do with this cocktail is do harm by diminishing the vaccine response. But again, this is a measure of whether or not the monoclonal antibody cocktail is doing harm, not a measure of the benefit that the monoclonal antibody cocktail is providing.

To sum up the serologic measures, when complete post-exposure prophylaxis is given with vaccine, wound washing, and a RIG or mAb cocktail, the early RVNAs levels are a contribution of the measure of the mAb cocktail's RVNA contribution, but the limitations are this is an indirect measure; it's serum, not tissue. There's no established protective threshold, and it doesn't measure the breadth of activity.

The late RVNA levels are a measure of vaccine interference, and one limitation that we

get into in the appendix of the backgrounder is that creative methods would be needed to measure this if the RVNA levels from mAb cocktail alone exceed the 0.5 international units per mL.

Ideally, we would be able to do randomized-controlled trials demonstrating the contribution of the mAb cocktail toward a decrease in rabies mortality, but this figure depicts the challenges that we're going to have in doing this. It's estimated that wound washing and vaccine alone lead to approximately 99 percent survival among rabies-exposed subjects. If you add RIG to the vaccine and wound washing, it's estimated that the survival rate increases to approximately 99.9 percent.

We want to make sure that the contribution that is shown in that little red line is not compromised by switching from the rabies immunoglobulin to a monoclonal antibody cocktail, and you can imagine the challenges that there are going to be doing this.

Even though the little red line is very

small compared to the contribution from the vaccine and the wound washing, it's still important. As Tanvir mentioned, 17 million people worldwide received PEP annually, so if you compromise that little red line portion, even if it's less than 1 percent of the contribution, you're still talking about death for tens of thousands of people.

Adding to the challenge the uncertainty regarding these estimates, the 99 percent and the 99.9 percent, it's probably greater than the contribution of the RIG component itself because these estimates are based on field trials and observational studies using different vaccines, different schedules, different RIG amongst subjects with different risk for rabies development.

If you think about it, subjects who have WHO category 3 rabies exposure are not a uniform group. They can have very different risks for rabies, and this depends on, first and foremost, the rabies status of the animal because if the animal is not itself rabid, of course there's no risk for rabies, and usually that's not known when somebody presents

for PEP; and the risks that the animal is rabid varies by geographic location, even in rabies-endemic areas.

Then the viral inoculum in saliva is important because even if the animal is rabid, if it doesn't transmit the virus, you're not going to get rabies. The bite location's important. As was mentioned earlier, bites closer to the head are much more likely to lead to clinical rabies. The severity of the bite's important, the number of bites, the depth of the bites. If you have a lot of bites and one is missed when they're doing the wound washing or administering the RIG, that can lead to rabies.

The time interval between the exposure and the administration of PEP is very important. It's universally recommended that this should be done as soon as possible, but the definition of prompt is not clear, so some studies define it as less than 24 hours. Others have gone out to 7 days, and that can make a big difference in the risk of developing rabies.

The type of vaccine and RIG used, the older varieties of vaccine and RIG are considered to be not as effective as the modern varieties. And finally, host factors. The one patient in the Iran trial who received the RIG and the wound washing and the vaccine and still died, did not have any detectable antibody levels after 7 days, so that patient might not have been a vaccine responder.

While we'd really like to have adequately powered randomized controlled trials with a mortality endpoint, placebo-controlled trials where we compare the monoclonal antibody cocktail with vaccine and wound washing to vaccine and wound washing alone would not be considered acceptable.

This was discussed at the 2017 workshop, and even though RIG is underutilized worldwide, it's still recommended worldwide. So representatives from rabies-endemic countries uniformly said that this would not be acceptable. But then noninferiority trials versus HRIG, even if with all the uncertainties you could calculate noninferiority margins, it wouldn't be feasible

because too many subjects would be required.

With our best guess estimates, we calculated that even if you restricted the trials to rabies-endemic countries with the highest rates of rabid animals, you'd still need to enroll over 50,000 subjects, and this just wouldn't be possible. So then we're left with demonstration of an acceptable survival rate for PEP, including the mAb cocktail. But then that leads to the question, what is an acceptable survival rate?

To examine this, we first looked at all the published data we could find on the survival rates for people with WHO category 3 exposures with any location bite in rabies-endemic countries who received PEP including RIG, and we found 18 studies, and we adjusted the denominator for any location bite and for the rabies status of the biting animal being unknown, and we came up with an approximate 99.86 percent survival rate, but there's a number of limitations with this approach.

The trials that we pulled went back to the 1950s, used different varieties of vaccines,

different schedules, different RIG, and our pooling approach might have led to some errors, too, but this is the best number we could come up with.

The observational data suggest that survival rate is even higher than 99.86 percent. The best data we have is from the Philippines where they have a large bite treatment center that in recent years has treated approximately 3500 people annually with WHO category 3 exposures with PEP including RIG. At that center, over a 14-year time period they've had 5 PEP plus RIG failures, which comes out to a failure rate of 0.01 percent or a survival of 99.99 percent. But of note, some of those 5 failures may not have been true failures because a few of them did not complete the vaccine series.

In the United States where 23,000 people annually receive PEP and there are between 1 and 3 rabies cases in humans annually, we don't know of any rabies cases in PEP recipients. But of course in the United States, most of these people probably didn't actually have rabies exposure. The

limitations of all the observational studies is that not all rabies cases may be diagnosed and captured. So if there was someone who died at home or someone who went to the hospital and the doctor didn't think about rabies, these might have been missed, and that would change these numbers quite a bit.

The next thing we had to think about in terms of an acceptable mortality rate is sample sizes that would be required to show this. Now, this table is not a table that can be used to plan a study because it doesn't take power into account, but it's a table that can be used that after how many patients who receive the mAb cocktail who are rabies category 3 exposures, died afterwards, you can use this to calculate the upper bound of the 95 percent confidence interval and demonstrate certain survival rates.

In this example, if you had zero rabies deaths out of 750 rabies exposed PEP plus mAb recipients, then the upper bound of the 95 percent confidence interval would be 0.49 percent. So you

could say that the survival rate is greater than 99.5 percent.

Now, if you wanted to actually plan a study that was adequately powered to demonstrate certain survival rates, you'd have to use this table. In this table, the first column are the clinically acceptable mortality boundaries that you would want to rule out, so this is what we'd have to determine, which one we want to rule out. The second column is the assumed PEP with mAb mortality rate.

Now for this, we thought 0.01 percent was a reasonable estimate based on the observational data in the Philippines, but it could also be a higher rate. And if it's a higher rate, the sample sizes go up quite a bit. The third column is the sample size is required to have at least 80 percent power and these were done in multiples of 500. So using this table, if you wanted to rule out a 0.1 percent mortality, in other words, if you wanted to demonstrate that the survival rate was greater than 99.9 percent, you would have to enroll 6,000

subjects to have at least 80 percent power.

One thing to note here is as you have a lower and lower clinically acceptable mortality boundary, the sample sizes go up exponentially. The other thing you have to take into consideration is ease of enrollment; so how easy will it be to enroll high numbers of subjects?

Unfortunately, with rabies-exposed subjects, I don't think it would be all that easy compared to other subjects because these subjects have to be treated quickly and could be spread over a large area. So they should be treated the first time they come into contact with a healthcare provider. So you don't have the situation you'd have with diseases like HIV where maybe a provider can see a patient and refer them to someone else to start a clinical trial because in this case there wouldn't be the time.

Now, there are large centralized bite centers that treat thousands of WHO category 3 exposures annually. However, most of these provide RIG and some of them free of charge, and you have

to think that if you're traveling through a rabies-endemic country, and you get bitten by an animal that you think is rabid, and you present to one of these centers, and they tell you, you can either get the treatment that's known to be effective or you can enroll in this trial and get this experimental treatment, would you want to enroll or would you allow your child to enroll?

The data we have on how feasible it might be is there was a rabies monoclonal antibody trial in India, and that took over 2 years to enroll 200 subjects as Dr. Bell mentioned earlier. Optimistically, there is now a report that a study with 4,000 subjects is planned in the same country where this monoclonal antibody is approved. So at least in the postmarketing setting, it's possible that larger amounts of patients could be enrolled.

The key question for today and for the clinical trials is how much confidence that survival is not compromised by the use of a mAb cocktail in place of RIG is enough confidence? You would need 6,000 versus 750 subjects to demonstrate

greater than 99.9 percent survival versus greater than 99.5 percent survival, and is the extra assurance worth it given the uncertainties and the added cost for development? On the other hand, is assurance of greater than 99.9 percent survival even enough?

Thinking about all of these uncertainties, we've come up with the following proposed approach, and this is what will be discussed today, so nothing is set in stone. This combines various components that each would contribute important information but that none of them would be sufficient on their own. The first would be the cell culture data that Damon described, and this would be the best way to show breadth of coverage against the diversity of rabies strains.

Then would be animal challenge studies that Dr. Ellison described, and these would be a good way to show survival benefit with the monoclonal antibody cocktail and also to get preliminary data to choose a dose. Then there would be clinical studies in healthy subjects, and this would be to

show that the monoclonal antibody cocktail has an acceptable half-life that it lasts long enough to cover that window period, acceptable early RNA levels, and accessible levels of vaccine interference.

Finally, we would want clinical studies in rabies-virus exposed subjects, and this would be to confirm the RVNA levels and the PK findings when the monoclonal antibody cocktail is administered in and around a bite and to support the survival benefit.

Now, details on specifically what we would like at the different stages -- and I've broken this up to prior to trials in rabies virus-exposed subjects and then from trials in rabies-virus exposed subjects. So prior to the trials, we'd like three things. The first is comparable breadth of activity against the diversity of rabies strains in cell culture studies for the monoclonal antibody cocktail versus a HRIG.

I've put up a hypothetical example here, and this is similar to the ones that Damon showed. On

tthe Y-axis, you have the antibody concentration over the EC50 value, and that's a logarithmic scale, and then you have a number of isolates on the bottom. In this hypothetical example, RIG is depicted by the diamond and the blue triangle is a monoclonal antibody cocktail, and you can see here that there might be some gaps in coverage for some of the bat strains, so this may not be acceptable.

The next thing we'd want is comparable survival in animal rabies challenge studies for the monoclonal antibody cocktail versus HRIG. Here is another hypothetical example, which shows percent survival on the Y-axis and time on the X-axis. The gray is animals that received the vaccine alone; the red is animals that received HRIG plus the vaccine; and then the blue dotted lines are various doses of the monoclonal antibody cocktail plus a vaccine.

You can see what the lowest dose of the monoclonal antibody cocktail that the survival is quite a bit lower than with HRIG, so that might not be acceptable. But the higher 2 doses here have

survival rates that are comparable or even higher than HRIG, and that likely would be acceptable.

The third thing we'd want is a comparable half-life, early RVNA levels, and levels of vaccine interference for the monoclonal antibody cocktail versus HRIG in clinical trials in healthy subjects.

Using the same figure that I showed before, which again is a hypothetical example, you can see that the half-life is long enough to cover the window period for the blue dotted monoclonal antibody cocktail; that the early RVNA levels are comparable and even higher for the monoclonal antibody cocktail in this example; and that at the later time points when the monoclonal antibody's contribution to the RVNAs has faded, that you still have a RVNA levels greater than 0.5 international units per ML, indicating that the vaccine interference is acceptable, so this might be acceptable.

The first topic for discussion this afternoon is the types of data needed to allow initiation of PEP with mAb cocktail trials in

rabies virus-exposed subjects and are the three described components enough?

For the trials in rabies virus-exposed subjects, these would be randomized-controlled trials of the monoclonal antibody cocktail versus HRIG, each in combination with thorough wound washing and rabies vaccine series in subjects with WHO category 3 rabies exposures predominantly in rabies-endemic countries. I say predominantly in rabies-endemic countries because if this trial was conducted predominantly in the United States, the mortality data wouldn't mean much because most of the subjects wouldn't have actually been exposed to rabies.

We would want these to start with lower risk WHO category 3 exposures in adults such as bites to the lower extremities, and then after an interim analysis, if there weren't any concerning findings, it should be expanded to include any WHO category 3 exposures, including high-risk exposures like bites to the head or neck and multiple bites. And we'd also like it to expand to include pediatric

subjects because roughly half of people who present for PEP are children, and ideally any product that was approved could be stocked by a health center and treat anyone who came in.

There would need to be a method to assess whether PEP was administered promptly and correctly at the time that PEP is given. We would not want this to be done retrospectively for any rabies deaths, so this would be something that we'd want to be done at the time so it can be looked at if there were any rabies deaths. Subjects should be followed for at least one year to look for rabies deaths.

The endpoints of these trials would be, first of all, confirmation of the following with the administration in and around the wound, comparable early RVNAs levels to HRIG, and comparable vaccine interference to HRIG. We'd also want comparable safety to HRIG and lack of rabies mortality.

This next slide shows proposed numbers. and again, this is a topic for discussion today. So

this is not set in stone; this is just to start the discussion. Our proposal for an initial submission for a mAb cocktail approval would be at least 1000 subjects to receive the map cocktail in total for the safety evaluation, and that could include healthy subjects who were not exposed to rabies.

The reason we came up with this number is, as mentioned before, the mAb cocktail will probably only help maybe 1 percent of people who receive it, so we don't want any significant safety concerns there in the same range. And if we enrolled a thousand subjects, that would be sufficient to detect safety signals with rates of 0.3 percent.

If we're going to require a thousand subjects for safety evaluation, it would be reasonable to expect 750 subjects with WHO category 3 in rabies-endemic countries randomized to the mAb cocktail arm. If we had this and there were no rabies deaths, that would indicate that survival is greater than 99.5 percent with use of PEP, including the mAb cocktail.

For postmarketing, our proposal is 6,000

total subjects with WHO category 3 rabies exposure in rabies-endemic countries who have received the mAb cocktail as part of PEP, and for this, subjects from the premarketing studies could be included in this total. Ideally, these would be randomized-controlled trials with disproportionate randomization to the mAb cocktail and HRIG for better context to interpret any findings, but this would not be a noninferiority trial.

The reason we chose 6,000 is because that would provide at least 80 percent power to demonstrate greater than 99.9 percent survival with use of PEP, including the mAb cocktail, assuming that the true survival rate is 99.99 percent.

This is the second topic for discussion this afternoon, which is the types of data needed to support a biologics license application of a rabies mAb cocktail for use in PEP and how much assurance that survival is not compromised by use of the mAb cocktail in place of HRIG is needed for the initial approval, and is needed for a recommendation as a first-line PEP component instead of a

recommendation for use only when HRIG is not available, and how much data should be collected pre- versus post-approval?

I'd like to thank the same people that Dr. Bell thanked earlier, and I think move into questions.

Clarifying Questions

DR. BADEN: Thank you, Dr. Troy.

This concludes the presentation component of the meeting. I would like to thank the agency for wonderfully framing a very complex set of issues, and Drs. Bell, Deming, Ellison, and Troy for terrific talks that really frame the challenge before us. And I think we all concur how important this issue is for the future of prevention in this space.

We have about an hour and a half for clarifying questions. In the clarifying questions process, I'd like to do two things. One is if you have questions, signal Lauren or myself, and we'll add you to the list. If in a particular line of question, you have a follow-on that builds on a

theme, take your card and flip it sideways, and that way -- we've done this in the past, and you've tried to signal me, and I couldn't sort out if it was to be added to the list or to build on a theme because where we can build on a theme, I think it's more advantageous than we're ping ponging around the same issues, and therefore not able to get to the bottom of it.

So please, it's probably best to take your card out of its holder, and then that can be a way to informally signal to facilitate discussion.

I would also suggest that we ask clarifying questions to Dr. Ellison first, if possible, so that we can keep him at the table for the rest of the discussion and not have him ping ponging up to the podium and be able to be part of the discussion, but I realize that may not be possible.

As you all are aggregating your questions and signaling Lauren and myself, I will start with a question to Dr. Ellison

The animal model, trying to sort out your being both a presenter and a member, which is an

unusual circumstance, but we're going to ask you to appropriately manage both duties. The issue of the animal model, you mentioned the hamster model as recapitulating the disease, the human disease, phenotype.

Which other models are you confident in to recapitulate the human disease phenotype and could be used as part of rigorous study?

DR. ELLISON: Well, rabies is a disease of animals, and they are the natural model systems for animals. So any of the reservoirs that maintain transmission could be used as an animal model. At CDC, we've used skunks, foxes, raccoons, bats, pretty much all of the reservoirs. But in terms of public health, I think probably in addition to the hamster, the best utility would be the dog model that's the natural reservoir and responsible for the most human mortality, globally.

DR. BADEN: Could you then envision studies in the hamster and dog model that could recapitulate human exposure and then the efficacy of the different PEP interventions in a systematic

way to demonstrate activity at least in those models?

DR. ELLISON: In terms of reproducing the exposure, we don't exactly recapitulate a bite, which is how the disease is transferred. What we do is an experimental infection, which is basically an infusion of the virus into the muscle, typically the gastrocnemius. That is a severe model of the exposure. We don't also do the wound washing or the other components of that, but we are able to cause an acute progressive encephalitis, which is rabies that is diagnosed using the standard methods.

What was the second part of your question?

DR. BADEN: What I'm getting at is can we have two or more animal models that recapitulate the human disease phenotype, that one could then study the role of the monoclonal antibody as being efficacious?

DR. ELLISON: Yes, you could use two animal models.

DR. BADEN: And the hamster and the dog

would be the most likely from your experience or the best representative.

DR. ELLISON: Yes, in my opinion.

DR. BADEN: I think Dr. Clark has a question.

DR. CLARK: Two things. I'm always wondering about how the animal model doesn't replicate the human experience in terms of the wound washing and whether the immunoglobulin may be disproportionally important in the animal model, if you have any thoughts on that.

DR. ELLISON: Well, we don't wash the wound because
we know the wound washing is pretty good at preventing disease; then we wouldn't be able to evaluate any biologic.

What was the second part?

DR. CLARK: Well, I was just wondering, basically, whether the immunoglobulin administration in animals may be disproportionally important compared to humans because of the lack of the wound washing.

DR. ELLISON: We do adjust for the weight-based dosing for the drug to be administered, but I think it would be a more severe model of evaluation because you don't know necessarily remove any of the initial virus that could be at the surface. It's an intramuscular infusion. Usually the bites are transdermal, so it's a lot deeper.

DR. CLARK: Then the other question I had was have you done studies looking at immunoglobulin alone with no vaccine, either HRIG versus a monoclonal antibody?

DR. ELLISON: There have been studies done with using HRIG alone, and they do show survival, basically.

DR. CLARK: Right. So has that been compared to any monoclonal antibodies in animals?

DR. ELLISON: Not that I know of, in the published literature.

DR. BADEN: Dr. Moore? Is Dr. Burgess a follow-on? No?

Dr. Moore?

DR. MOORE: Hi, Dr. Ellison. You mentioned that different strains do not induce a hundred percent mortality in the hamster model. Would that limit the use of a hamster model or do you have certain ways to control for that or adjust to that?

DR. ELLISON: No. That's a great point. Rodents are not a natural reservoir of rabies, so it is kind of artificial using them to start with. We use them because they are laboratory bred, so we're able to have sufficient numbers and also a standard model. But yes; if it doesn't cause mortality from a peripheral route, we're not able to evaluate that isolate.

In terms of collecting these primary isolates, the best model is to use an actual homogenate of salivary gland from a rabid animal. That's basically as close as you can get to representing a bite. But if you need to amplify that virus in cell culture, we do know that there are laboratory artifacts that are induced that may or may not influence pathogenesis. They might have an abortive infection in the periphery,

seroconvert, and survive.

DR. BADEN: Dr. Green?

DR. GREEN: This is the logical follow-on to the first two questions you addressed. You just told us that we have two options that were viable animal models, and you just said that if we use the hamster, it has some limitations because it doesn't cover all potential strains. But if you use both models, do you then think you adequately account for essentially all of the strains?

DR. ELLISON: I was asked to propose two models. I think one model is sufficient. If we're not able to cause mortality in a hamster model, I think you would have even less likelihood causing mortality in a dog model.

The diversity of rabies virus is greatest in the Americas. Overseas, typically what they have is dog rabies and other lyssaviruses. I think it's important to look at the epidemiology of human disease. Some of these rare and obscure variants have never caused human disease or may not even have exposed people. I don't think that we should

focus extremely on them because of the likelihood of them actually causing diseases unknown.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: First for Dr. Ellison, but maybe Dr Deming for this question. And the question is whether or not there is any evidence that you're aware of that antibodies that might not neutralize in an in vitro assay have an apparently beneficial effect in an animal mortality model.

DR. ELLISON: So you're right. When we use a polyclonal product that's from hyperimmunized to people such as HRIG, there are antibodies that are produced to matrix protein -- other proteins. The only beneficial one is the glycoprotein, the exterior antigen.

We don't necessarily know what is the impact of those other antibodies, but I can extrapolate that to animals using -- USDA does an oral rabies vaccination campaign through the United States where they use a recombinant vaccinia virus that incorporates the rabies glycoprotein in it. That's the only antigen associated with rabies that's in

that vaccinia vector that's distributed as bait. We do show that that is effective, so that kind of gets at glycoprotein is the most important.

DR. BADEN: You can do your follow-on, and then I'll do mine.

CAPT BURGESS: Thanks. The reason I asked the question is that if you're specifically considering how you might put together a package for the approval of a combination of monoclonal antibodies, there's extant evidence that in a completely different disease process with completely different monoclonal antibodies, an antibody component that does not appear to neutralize in the available in vitro assay is nonetheless essential for a protective effect in an animal model that was thought to be relevant. So that's not lyssavirus at all.

The question is whether or not has anybody looked, that you're aware of, at the effect of an antibody that would have failed a screen in a neutralization assay?

DR. ELLISON: I don't think I quite

understand your question.

CAPT BURGESS: So a mAb that that did not appear to neutralize in an infectivity assay in vitro, has anybody ever looked to see if it had an effect in an infection model with a mortality --

DR. ELLISON: Like does it generate an escape virus?

CAPT BURGESS: Or would it work when it would not have been predicted to have worked?

DR. ELLISON: Yes, not in the published literature that I can tell you, but just by experience, you can over-saturate it, and it might have some reduction but maybe not complete neutralization.

DR. BADEN: So another follow-on. You say the antibody to the glycoprotein is the key. How well is that established in the human model, or what is the basis on that? Because I think the polyclonal has a broad array of epitopes, even though they may be subdominant, or less prevalent, or have lower affinity.

How would we establish that the antibody to

the glycoprotein is truly the key in the human model?

DR. ELLISON: I think they've done deletions with glycoprotein and shown that it can't actually enter a cell without that glycoprotein, so that establishes its correlate for pathogenesis.

Also, we know by electron microscopy in other studies that it's the only external antigen that's even exposed on the surface of the virion. And you have to have that glycoprotein to be infectious, so I think that inherently it's the most essential because it's the only one on the outside.

DR. BADEN: Sure. And I don't disagree with the importance of it. It's just whether or not there are other epitopes that may contribute to a protective immune response beyond the glycoprotein.

DR. ELLISON: I'm sure there are, but that hasn't been thoroughly investigated.

DR. BADEN: Dr. Deming?

DR. DEMING: So I don't know the answer to this, but I think to word the question differently,

are there any antibody mediated functions other than neutralization that might be involved in protection?

DR. ELLISON: I'm sure there are. There has to be a T-cell mediated response to the innate immune system. I think the impact and utility is less than that of the antibody.

DR. DEMING: But the point that Dr. Burgess made is good, that a neutralization assay is only going to look at neutralization, not at any of these other --

(Crosstalk.)

DR. ELLISON: Correct.

DR. DEMING: -- Fc-effector functions.

(Crosstalk.)

DR. BADEN: Dr. Moore?

DR. MOORE: There are studies that show that anti-glycoprotein antibodies may differ a little bit on how effective they are in neutralizing. When we measure the immune response to vaccination by ELISA that's directed to the glycoprotein, it's not always equivalent to the neutralizing or the

RFFIT results. In some patients, you can have a high glycoprotein binding antibody in the mix that may not be as neutralizing. So um, there is a variation of how well that anti-glycoprotein antibody can neutralize.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Thank you. I'd also like to thank the FDA, as you did really excellent presentations that were just spot-on, I thought. My first question is for I think Dr. Deming or Dr. Ellison.

Dr. Deming, there was a slide 21, which showed the difficulty interpreting I guess the cell culture assay in terms of whether you get a green light, so something like this. And we have a bar there at zero, but as was mentioned earlier, there is no correlate of protection for passive immunization. And if we had a correlate of protection for passive immunization and thus could draw a dashed line up there somewhere, it might help to interpret a figure like this.

So I was wondering if in the hamster model

one could give varying amounts of antibody and thus find the point at which you had 99 percent protection or whatever, and thus define a correlate of protection using an animal model experiment to help draw a line there to help interpret this data.

So the question is whether you could have varying amounts of monoclonal antibodies in the hamster, and from that to find a correlate of protection for the hamster, which might help interpret a slide like this, or have such studies been done?

DR. ELLISON: Yes, there's been dose studies done, and there is a dose effect based on the amount of monoclonal.

DR. FOLLMANN: So there is a dose. So for existing data or for the new candidate, monoclonal antibody, such studies could be done, and they could be used to help interpret data like this.

DR. ELLISON: Correct.

DR. BADEN: And you're doing challenge studies not just with the CVS-11, but with all of these --

DR. ELLISON: CVS-11 is a laboratory adapted strain that grows in cell culture. It's doesn't cause mortality, typically not.

DR. BADEN: But the CHALLENGE studies in the hamster are with the whole list of isolates here --

DR. ELLISON: Yes.

DR. BADEN: -- or could be.

DR. ELLISON: When they're able to cause mortality, yes.

DR. BADEN: Dr. Moore?

DR. MOORE: I just want to make another comment. When you give the dosage, and you determine what dosage is effective in the animal model, you're looking at two different monoclonals, and you say this dose is good and then this dose is good.

Does that correlate to the in vitro measurement? In other words, talking about this graph here, if you give a 1.25 and it gives good protection, and you get 0.25 and it gives protection, when you measure the antibody at

different time points, will it be equivalent? Will it be the same?

DR. ELLISON: That's tricky because when you infect, you're going to also produce antibodies against that challenge virus itself, so it is confounded. When you're talking about, for instance, like a cocktail of 2 mAbs, you separate and do independent challenge studies using each one of them separately.

For instance, like with this tricolored bat variant here, yes, one of them protects, essentially, and the other one does not because it's not directed against that epitope. They correlate with the cell culture data in vitro, but you do have confounding factors associated with the challenge itself. You wouldn't give this in a pre-exposure scenario, so it's hard to imagine or even calculate what the therapeutic level would be in the hamster at the time of exposure.

DR. BADEN: Dr. Weina?

DR. WEINA: [Inaudible - off mic] -- mortality at all, and are those

principally -- I mean, obviously they're known somewhere, but are those principally bat isolates, or are those terrestrial isolates, or are those -- we wouldn't necessarily be chasing after a very, very, very unlikely exposure.

So the question becomes which ones are we missing in the hamster model because they don't cause mortality, and should they be things that we do have to think about a second animal model?

DR. ELLISON: The greatest diversity of lyssaviruses in the U.S. is detected in bats. And even in the terrestrial reservoirs in the U.S., skunks and foxes and raccoons showed diversity within the lineage that they transmit, and they're the ones that are most likely to be exposing people.

I think it's important -- rabies has been a national notifiable disease since inception of the program, and I think it's important to look at the epidemiology of human associated disease that it is caused from that. Over the past 90 years in the U.S., we've had 60 human rabies deaths, and the

majority of them are associated with bats. We've been able to isolate the virus and type it, and have shown that it could potentially cause mortality in the hamster model, but not always. But that's because there are certain artifacts that are introduced when you're amplifying these viruses in cell culture that may influence pathogenesis, So it's not a direct comparison.

DR. WEINA: I'm sorry. If we're missing them in hamsters, there are necessarily no other animal models that they would cause mortality in?

DR. ELLISON: Rabies is a disease of animals, and they are susceptible to pretty much -- every animal's been susceptible, that they've tried with different viruses. I don't know if you would necessarily be able to call -- I don't know if one model is more sensitive than the other.

DR. BADEN: Dr. Clark?

DR. CLARK: So just to clarify that, you're saying there is some bat rabies from the U.S. that wouldn't necessarily cause disease in the hamster?

DR. ELLISON: When it's inoculated

experimentally, it results in an abortive infection.

DR. CLARK: Then how about rabies from areas where these vaccines would likely be studied, so Africa and Asia? Would most of those be replicated in a hamster model or would there be big holes there?

DR. ELLISON: Well, that's a whole different story because rabies virus, as we're talking about it today, is only in bats in the new world. In the old world, there are other lyssaviruses, and they're not efficacious against our biologics at all. What they have outside of the Americas is dog rabies, and dog rabies is pretty phylogenetically succinct. There's not much variation in it. The greatest variation is in the new world, the Americas, associated with bats.

So overseas, you would be exposed typically to a terrestrial reservoir dog, jackal, hyena, or something like that, and they transmit rabies virus. I don't think anyone's mentioned it today, but rabies is a disease caused by a virus,

lyssavirus. There's actually 14 recognized lyssaviruses now. Only the genotype 1 rabies virus is in North and South America, in bats.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Yes. Just clarifying, does the hamster model work for the dog rabies virus that is in most of the world?

DR. ELLISON: Yes. The hamster model works very well for the dog variant --

DR. GRIPSHOVER: Okay. Great. Thanks.

DR. ELLISON: -- which we do not have in the United States. We've eliminated it.

DR. BADEN: Dr. Bell?

DR. BELL: Dr. Ellison, you did mention a bat model. What are some caveats to the bat model challenges? I would assume that's a difficult model to use.

DR. ELLISON: We use the bat model to study pathogenesis and transmission and evaluate new vaccines that could be used to prevent rabies. In large colonies, bats are gregarious. They live in colonies numbering thousands. Within that colony

of a thousand, there might only be 2 or 3 rabid individuals that are capable of transmitting it to the others. So the question is how do we stop that transmission.

The bat model -- bats have a unique physiology that does not replicate human anatomy. They use torpor, which is a form of hibernation over winter. Their reproductive cycles are different, so I think the extrapolation to human would be a little bit more of a reach.

DR. BADEN: Follow-on?

MALE VOICE: No, no.

DR. BADEN: Then Dr. Ofotokun?

DR. OFOTOKUN: This has been a very interesting discussion and presentation. I think my question might be a little bit naive because it seeks clarification. It does appear that the current standard of treatment for rabies, for rabies work most of the time, is we're trying to improve on this. From the materials you provided, there are definitely advantages of the monoclonal antibody as compared to the conventional

immunoglobulins.

The question I have is rabies is mostly a disease of the central nervous system. In your animal model, can you just clarify how well monoclonal antibodies penetrate the blood-brain barrier?

DR. BADEN: I guess that's a general question to our presenters and experts.

DR. ELLISON: Yes. I think that the best utility of monoclonal antibodies should be at the local site of exposures. So it's not going to necessarily need to penetrate the blood-brain barrier. Actually, HRIG or any type of post-exposure prophylaxis is contraindicated once clinical signs appear in humans.

DR. BADEN: Is there any reason to believe the monoclonals won't behave like IgG in general? Dr. Troy?

DR. TROY: I don't think we know of a reason why the monoclonal antibodies would act differently than IgG in general. And to follow on, when the virus reaches the brain, it's too late. That's

when you have the clinical disease.

DR. DEMING: It is related to the issue we discussed earlier. We don't know if there are effector functions that antibodies mediate other than neutralization that we might not see when we're just --

DR. BELL: And in the clinical -- sorry. In the clinical scenarios, even if it's late, I've read case reports where in the hospital, they give the RIG product in addition to the vaccine just in case. So it's hard to tell in humans if it's artifactual or if it's really causing anything, doing anything.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: This is a question I guess for Dr. Bell. We're asked to opine on this and looking at various metrics with similarity between the immune globulin and the monoclonal antibodies, including serology and similar lack of mortality. In other diseases, like HIV, for example we have surrogates of disease like viremia or CD4, and you haven't mentioned anything like that.

I know there's no viremia in rabies, but for completeness, I was wondering if thought had been given to some kind of surrogate of disease. For example, I saw in some of the information that this virus will travel like 10 to 100 millimeters a day. If you could measure that, maybe that could be a measure of rapidity, and you might try and compare that between the two groups.

There could be an immune signature that you could look that's associated with rabies disease beyond the monoclonal antibodies, and if there's more of this immune signature, or if this immune signature is similar in the two arms, the immune globulin and the monoclonal antibody arm, that would be reassuring as well.

So the bigger question is surrogates would beyond what you have, like disease or immune signatures, and I was wondering if you had thought about that or if that's a possible avenue?

DR. BELL: That's an excellent thought process and excellent question. To my knowledge, there's no other surrogate marker, and rabies

doesn't cause viremia like you suggested. It would be wonderful if we had a viral load test analogous to HIV or hepatitis C, but we don't have that. I didn't look back at how they got that rate of trans --

(Crosstalk.)

DR. FOLLMANN: I was curious about that.

DR. BELL: -- but I can certainly look at that.

DR. ELLISON: They severed the nerve and tested it, so it's a destructive technique.

DR. FOLLMANN: So this would be in animals.

DR. ELLISON: Yes, it was a serial sect done in animals.

DR. FOLLMANN: Unless you want to lose your nerve.

(Laughter.)

DR. BELL: That's right.

DR. ELLISON: But we know that's effective in preventing rabies, but it's not very practical.

DR. DEMING: Just to follow up, it would be great if there were such a surrogate, but there

isn't one. And we can't even tell with certainty who has actually been exposed to virus versus who has not if the attacking animal can't be isolated and tested.

DR. ELLISON: Also, there's a difference in the amount of virus actually -- we don't know how much virus is transferred from the bite of a rabid animal. And the bite of a rabid animal from a dog to a bat is very different, the amount of saliva transfer. So we don't actually know the effective dose needed to cause disease.

DR. FOLLMANN: I sort of have an add-on -- this is moving in a particular -- if I could.

DR. BADEN: Dr. Green?

DR. GREEN: If you're looking for a methodology, you talked to us briefly about the bioluminescence mouse model, and the pictures seem to look like you could track it, and your bullet point says allows real time visualization of dissemination. Would that be an opportunity for a way of looking at -- I know it's expensive, but

looking at pace over time?

DR. ELLISON: So really, when it gets to that CNS, it's too late. What you're looking at is an ex vivo and in vivo picture. The ex vivo picture was at euthanasia. That's actually deflected open. And if you look there, too, you see the sciatic nerve is exposed. That animal is infected in the gastrocnemius, but for some reason, there's not luminescence observed in that sciatic nerve.

We don't know if it replicates at the site of exposure or not. We do know that the replication of rabies is very tightly controlled to be as low as possible. If there was a lot of replication, you would trigger an immune response; you'd abort the infection.

DR. BADEN: Dr. Follmann, did you have a follow-on or an adjunctive question?

DR. FOLLMANN: Yes. I think it's a bit different from this current line, so I would defer my question.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Just the concept of being too late, in the real-world scenario, when people are bitten, especially in resource-limited setting, people are going to be presenting at different times. So people would come in immediately after the bites. Some may come in 2, 3, 4 days after the bites.

So no matter what we do, that has to be taken into consideration. There has to have been some level of establishment, or maybe in apparent asymptomatic infection in the nerve, it may not have gone to the central nervous system, but at least it has to have been some level of establishment of an infection by the time of presentation.

DR. BADEN: Dr. Bell?

DR. BELL: When we're proposing trials in rabies-exposed patients, we would think that people should come and be enrolled in a trial within 72 hours. Usually that's what's suggested, but we do know that people report after that. Another consideration is rabies exposure in a rural area

versus a central area. Obviously, in a rural area, in an endemic country, it would be hard to get timely administration.

DR. BADEN: Follow on?

(No response.)

DR. BADEN: Dr. Ellison, thank you.

DR. ELLISON: Thank you.

DR. BADEN: You can join us at the table. We may still have more questions for you, and you will have to jump between your visages.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: It's for Dr. Ellison. So building on that, have they looked at timing in the hamster model of when it's too late for even the RIGs to work in terms of preventing mortality; like if you inject the hamster and 3 days later it's too late? Have they looked at timing of the immunoprophylaxis?

DR. ELLISON: Typically, with the studies that I'm familiar with, they give it at 6 hours or 24 hours post-infection. Your question would be, so once it already gets to the spinal cord, say the

thoracic area, and you initiate PEP, then how effective is it at preventing disease?

DR. GRIPSHOVER: Yes, or even -- I guess there or at what point? To be able to get some idea of when it's too late in the field or not? It's more for how it would be rolled out and not so much how you would do a clinical trial. Obviously, you want to standardize it as best you can for a clinical trial, but in real life, people are going to show up late. When is it too late, and in animal models, have there been any studies to look at the varied timing?

DR. ELLISON: No, and I think there are a lot of variables there: the site of exposure; how many bites the infectious virus has actually transmitted. You're going to develop rabies a lot quicker to a severe facial exposure than you would to the leg. That hasn't been evaluated sufficiently. There are too many questions.

DR. BADEN: Dr. Porter?

DR. PORTER: Thank you. I have a very basic question. If there's such high success with the

HRIG, why are we looking at monoclonal antibodies? Will it decrease the cost of manufacturing? Will it change how it is stored so it's readily available in the poorer countries that don't have the refrigeration?

That was basically -- I just want some clarification about that.

DR. TROY: Thanks. The reason to develop them is different globally than in the United States. Globally is where it's most needed because that's where RIG is underutilized the most. In the United States, the only advantages would be in case of potential shortage of HRIG, to try to prevent a shortage, and because of the theoretical risk of transmission of bloodborne pathogens, which hasn't been seen with HRIG in the United States. But there is a very big advantage globally, and we don't know if they could make them more cheaply or if they could make products that wouldn't require the cold chain or things like that, but that's where it's most needed.

DR. BELL: So I looked up the HRIG approval

yesterday, and once the HRIG is taken off the shelf and unfrozen, it has a 1-month half-life. Robin was going to help me look it up, and she found some more information about the monoclonal antibody, but I think monoclonal antibody would be in a vial and could be stored at different ways. Some part of the storage would be the same as HRIG, but I would think it would have more of a shelf life.

Robin, can you add more?

DR. SCOTT: I would say the shelf life of HRIG, I believe, is 36 months if I'm not mistaken, and that's 4 to 8 degrees. However, there are a lot of stability studies that are done at accelerated conditions, and perhaps that's what you're referring to; for example, a temperature of 42 or even 60 degrees.

The actual studies you probably want for a tropical temperature range, that may have been approached in some very old studies of the HRIG that's been around for a long time, and we can look into that, because most of these that are manufactured in a modern fashion do have a longer

half-life than 1 month. So I'm sure that HRIG has a longer half-life than one month unless it's stored at, say, 60 degrees.

We can look into that, but I don't know if I can get the answer for you by the afternoon.

DR. BADEN: A follow-on, how well do we know HRIG has activity for the global diversity of the strains that infect humans? For those who are not at the table, when you come to the mic to provide information, please state your name for the record so we know who is providing information.

DR. SCOTT: Will you repeat the question?

DR. BADEN: So my question is, with HRIG, much of our morning discussion was looking at the global diversity of rabies that has infected humans across different animal reservoirs or animal species that bite. How do we know HRIG is active against all of those different strains globally that cause human disease?

DR. SCOTT: Well, I think that's actually probably a better question for Dr. Ellison because HRIG that we have licensed now is not studied in

that fashion. It was studied for the U.S. market, and there are published studies with at least one of the HRIGs with that information.

DR. BADEN: A procedural issue --

DR. SCOTT: Dorothy Scott, by the way, FDA.

DR. BADEN: Thank you, Dr. Scott.

Dr. Ellison, I apologize, but when you answer questions as an expert, we need you to stand. You can go to the mic. Hopefully, we can give you a hand mic. When you are a panel member, you get to be seated.

(Laughter.)

DR. BADEN: I apologize, but that way, there is clarity as to how the information is being shared and under what frame. Thank you for working with us.

DR. ELLISON: I think one of the best examples of the benefit of HRIG is that we haven't had a failure in the United States associated with those individuals exposed that received cell culture vaccine and immune globulin in the United States. So we've never had a post-exposure

prophylaxis failure.

DR. BADEN: Aren't there human infecting isolates that are less susceptible to HRIG, or has that not been observed?

DR. ELLISON: It's not been observed, but that's also why you've got a two phase, a passive and an active component.

DR. MOORE: I can only speak to cell culture. When we use HRIG as a control when we're looking at monoclonal coverage, what we have seen is that there are some bat strains that HRIG is not as effective against as some terrestrial strains. So there is a difference, even with HRIG -- I'm talking cell culture -- on how effective it is.

DR. BADEN: Dr. Harrist?

DR. HARRIST: Thank you. I just wanted to follow up on Dr Troy's answer to Dr. Porter's question in that cost, for us anyway, we still see it as a barrier in the United States to get HRIG. Or at least in my state we definitely had people delay their vaccinations because of concerns about how much it cost, especially if they're uninsured,

and also for our rural critical access facilities to stock it, given that they may not get to use it before it expires.

So I just wanted to clarify. If you mentioned it, I'm sorry, but I missed it. Do we expect that the monoclonal antibodies will be less expensive than the HRIG?

DR. TROY: We unfortunately have no control over that whatsoever. We hope that it will be less expensive, and that's what's been given as a reason to develop them, but we don't control costs.

DR. BELL: In fact, WHO provided tech transfer, so they ended up giving some monoclonals to various industry with the hope that eventually it would be given at a cheaper cost. So that it is the hope, but there's no promise.

DR. BADEN: Dr. Porter, do you have another follow on?

DR. PORTER: I do. If compliance is a problem
in the administration, correct administration is a problem with the HRIG, how is having a monoclonal

antibody going to address that issue?

DR. BADEN: Dr. Troy?

DR. TROY: I don't think it would.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: Thanks very much. A follow-up to Dr. Porter's question that most of the advantages would really accrue benefit outside this country, to resource-limited settings. And given that, does FDA envision that the entire clinical studies in rabies-exposed people could take place outside the United States, or would there be regulatory or ethical requirements that would require it to also have a site in the U.S. participating?

DR. BADEN: Anyone in the agency wish to respond?

DR. MURRAY: Well, my opinion is it would be optimal to have some U.S. sites. Usually, we try to have U.S. sites in clinical trials to have some representation, even if we expect most of the endpoints or treatment effect to be demonstrated outside. So I think it would be optimal to have at

least some U.S. sites.

DR. BADEN: Dr. Clark?

DR. CLARK: Just a follow-on in terms of logistics for Dr. Troy. When you mentioned the Indian study and the slow accrual, do you know the reasons for that? Was there reluctance on the part of patients to consent because they perceived a difference in the antibody products?

DR. BELL: There were some local issues in India where there was some distrust with clinical trials for a while, and also people were also very poor and illiterate. So at one point within the trial, they actually had to do video consents. So there are issues such as that, that I heard them at the public workshop with the Indian trial.

There are a lot of issues that went into that. As Dr. Troy mentioned, it's hard to ask for consent. Many areas of the world that are rabies centers, which would be optimally where trials would be done, Those are the places that provide HRIG free of cost.

DR. CLARK: So the Indian study wasn't done

at a rabies center or rabies centers. How would you envision this to be different with any new trials, those barriers?

DR. TROY: I think some of the barriers were unique, and it was the first trial of a clinical trial in rabies-exposed subjects of a monoclonal antibody. That was done at 5 sites. I do think it's optimistic that they're planning a trial in 4,000 subjects. They must think it's more likely now; I mean, more possible now to do higher numbers.

DR. BELL: There would be local factors, too, because some countries, the IRB may not approve, for example, placebo controlled -- which we're not saying is the case; that's just an example -- as to what would be ethical within those different countries. So there are other factors beyond what we can control in the U.S.

DR. BADEN: Dr. Baker?

DR. BAKER: Thank you; following up. Can you talk a bit about FDA's experience with clinical trials of this magnitude that would be required

overseas to address some of the feasibility issues?

DR. TROY: With other products, with vaccines in particular where they're given for prevention, they can have trials with hundreds of thousands of participants. For HIV trials, it's typical to have 1500 participants. This is a unique situation because it's both for a prophylactic drug where typically you have larger numbers of subjects, but you have to treat it or administer as quickly as possible with all the challenges we talked about before.

DR. BIRNKRANT: As was mentioned, we do accept foreign clinical trials. As far as foreign clinical trials are concerned, ideally they should be conducted under an IND. They don't necessarily have to be, but I think in this particular case, given various ethical issues, trying to ensure that there's adequate informed consent, we would be most appreciative and would encourage sponsors to -- if they wanted to conduct their trials outside the United States, at least conduct them under an IND.

All clinical trials, once they came in as

part of a marketing application, we would then go out to the field and do inspections to ensure that the data are robust and accurate.

DR. BADEN: Do you have a follow-on?

DR. BAKER: Thank you. Do you have specific experience with healthy volunteer trials of this size that's also required for overseas in terms of all the feasibility and the ethical considerations that could help us inform the likelihood of success of a proposed clinical?

DR. BIRNKRANT: The HIV PrEP trials were quite large, and the number of the trial sites were outside the United States.

DR. BADEN: With thousands enrolled.

DR. BIRNKRANT: Right. There are other indications, even outside of our Division of Antiviral Products, where trials are extremely large. Drug development today is global, frankly, not just for infectious diseases but for other indications as well. So I think the agency is quite familiar with how to proceed in the global arena.

DR. BADEN: Dr. Green?

DR. GREEN: So this gets to the follow-on, to the question of this being done out of the United States. I have a simplistic question, maybe because it doesn't reflect my understanding. FDA is holding these hearings because they're contemplating giving approval in the United States, so I wonder, given that in the rabies endemic countries, they have dog rabies, and in the United States we don't have dog rabies.

Can we extrapolate protectiveness achieved in an environment that's dog rabies when we have more of an issue with bat rabies in the United States?

DR. TROY: That's where the nonclinical studies are going to be so important, the animal studies and the cell culture data. We would, again, enroll some people in the United States, but most of the data to support the strains that are in the United States would be from the nonclinical studies.

DR. GREEN: Right, but I guess I'm still

left with if you say that the four steps include human trials to give assurance for FDA approval, the fourth step, wouldn't it seem, give assurance that it would be effective in exposed humans to bat exposure?

Unless I'm wrong. You could have all the other steps, but you're requiring the fourth step to get approval, but the fourth step isn't really, it seemed, testing the exposure that we have, that tests the exposure, that places like India have.

Is that right?

DR. TROY: I want to bring up one point about a third of the rabies cases in the U.S. are from people who travel abroad and get dog rabies and come back. So we do have to worry about dog rabies in the United States, too, so it's not just the bat. We are extrapolating from the clinical data that if it works against dog rabies, and if we also have the cell culture and animal data showing that it has activity against the other strains, that would work against the bat strains, too, yes.

DR. BADEN: There are 6 people who have

claimed follow-on. Dr. Follmann?

DR. FOLLMANN: My follow-on is a little different than -- well, it's a follow-on from five minutes ago. I was interested in the -- this would be for Dr. Bell or Dr. Troy. It's about the 200-person trial that was conducted in India and also the 4,000-person trial.

Did one of those result in licensure in India where they randomized with a superiority? Those kinds of details, what's the endpoint?

DR. BELL: Yes. The trial in India amongst the 200 was randomized. They did start with lower severity bites in the leg, and it was approved in India in 2016.

DR. FOLLMANN: And what were the arms then; a monoclonal versus RIG?

DR. BELL: HRIG, yes.

DR. FOLLMANN: So 200 got approval, like a hundred in each arm. And the endpoint was what; serology and I guess lack of mortality?

DR. BELL: Exactly. Serology was the main basis of approval, but also they assessed for

mortality, which wasn't much, and then also the safety was seen, the monoclonal with the local reactions and things of that nature.

DR. TROY: Tanvir, there was no mortality in that trial but there are big differences in that if we're talking about a country where RIG is underutilized, then I think the standards for approving something would just be that it caused no harm. So their main endpoint was the late RVNA endpoints to show that it didn't have the vaccine interference. But of course in the U.S. where HRIG is used most of the times when people present for PEP, we'd have to have a higher standard.

DR. FOLLMANN: So was hand washing, vaccination, and antibody used in the 200-person trial, or was it --

DR. TROY: Yes.

DR. FOLLMANN: -- so they used all three.

DR. TROY: Yes.

DR. FOLLMANN: The final thing, the 4,000-person trial I guess is similar kinds of studies randomized to monoclonal versus HRIG, each

RIG?

DR. TROY: So our information on that was actually just a publication for the World Health Organization saying that one is planned, so we don't have any more details on that.

DR. FOLLMANN: Okay. Thanks.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: The issue of logistics of doing this type of study in Africa, India, or wherever, where we typically have challenges with people consenting, lack of trust in the system, I'm having difficulty wrapping my head around the selling point here because the current standard of care works so well, and the disease we're talking about is so fatal.

How do you sell that, that we have a system, a standard of care that is 99 percent effective, but we want to try something that could add maybe an additional 0.5 or 0.1 percent to that effectiveness? How do you sell that in places where there is lack of trust?

DR. TROY: Ideally, these studies could be

done in a place where RIG isn't available or isn't utilized so that all the study participants would benefit. But this is something I think that the people who are developing the drug, those are challenges they're going to face in doing this, because the easiest places with the most infrastructure would be the ones where it'd be more likely that RIG is already available, and the ones that have less infrastructure where it would be harder to do trials would be the ones where it's not available.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: The other option might be that ERIG might be cheaper versus HRIG. So that other option would be to compare. For the applicability in the United States, we'd want to compare against HRIG, but ex-US, if they have to give ERIG versus monoclonal antibody, that's another possibility. But again, for the U.S. population, it would have to be HRIG versus monoclonal antibody.

DR. BADEN: Dr. Birnkrant?

DR. BIRNKRANT: I think you're bringing up very good points with regard to conducting trials in resource-limited situations, but the actual purpose of this meeting today is to try and get a path forward so that we can relay this information that we glean from you to potential sponsors so that they can embark on the process of trying to develop this important drug area.

You raise a very key question about how to, quote, "sell it" to the population, so I think that's something we need to think about more, and then we need to bring that to the attention of drug developers as well. But it's our understanding that the need for this product resides heavily on the fact that there could be potential shortages, and we want to be prepared for that type of situation. The shortages could occur in the United States, not just outside of the United States.

As my team members said, we don't get involved in cost, but with modern manufacturing and other positives of developing drugs at this current time, maybe it is possible that there could be a

price differential. I don't know. But in general -- not in general, specifically, we don't get involved in that.

DR. BADEN: But this is in the back drop of 59,000 deaths a year from rabies.

DR. BIRNKRANT: Right. So it's a public health problem, Maybe not as large of a problem in the United States, but worldwide it's a problem, And we are involved in global drug development at this stage.

DR. BADEN: Dr Gripshover?

DR. GRIPSHOVER: it was in part answered. That's why I kept putting it up and down. Part of how to get to in terms of a study design, if there are large populations in the world that don't have access to RIG right now, they would be potentially a good place for studies because it would be a win-win for both arms because they both would be getting something more.

So I guess that -- and there are there, then, large places that are. It's just that there's not the infrastructure. Is that a barrier

right now?

DR. TROY: Ideally, it would be done in a situation like you said, where it's in a place where people wouldn't get RIG, so then it may be a benefit to either arm. I do know the places with the most infrastructure provide RIG, but in terms of whether there are places that have enough infrastructure to do the trials that don't provide RIG, that's actually beyond what we know at this point.

DR. BELL: Some places provide RIG, ERIG or HRIG, to those only at poverty level. And for those minimally above poverty level, some of them may have to pay. India, for example, I think they provide it only for people under poverty level. I don't know if that would be an opportunity to get people enrolled in a trial.

DR. BADEN: Definitely challenging.

Dr. Birnkrant?

DR. BIRNKRANT: One more point, please, and that is with trials being conducted under an IND, we have the opportunity to review and provide

comments, and we will ensure that these trials are done ethically so that all participants are offered the appropriate treatment or prophylaxis.

DR. BADEN: Dr. Siberry, thank you for your patience.

DR. SIBERRY: Of course. Dr. Green had talked about what might end up happening, which is the trial pre-registration will largely depend on data that come from participants outside the United States and how does that then match with our intention for FDA to license it for use in the United States.

I just wanted to offer that this is really where I think a robust postmarketing requirement for that product, when it's used in the United States, would help address that, because I think it's probably not feasible to address it pre-registration.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: I'm a little unclear as to exactly the unmet need. Several things have been mentioned, and they seem to have been not

considered that important, such as the fact that cost isn't really the thing that's being considered here. We have existing treatment that is virtually 100 percent effective.

Safety is a theoretical concern but doesn't seem to have had a practical effect or relevance. So the availability underutilization and shortage of HRIG in limited resource countries has been mentioned. It's not clear to me what those factors are and whether they wouldn't apply equally to any product that has the same or similar storage constraints.

Also, the final thing that's been mentioned is the possibility of a shortage of HRIG, but given the variety of similar and also different issues with maintaining stocks, perishability, production of monoclonal antibodies, I'd like someone to really clearly lay out what the unmet need is that's going to be differentially fulfilled by this new product.

DR. BADEN: Dr. Troy?

DR. TROY: I can start commenting on that.

I'll start with the U.S., where Dr. Bell talked about how HRIG is produced, where you have hyperimmunized volunteers. You take their plasma. You pool it. You take out the HRIG. They do a lot of these. The three manufacturers keep a stockpile of the serum, so you don't have to go through the entire process to ramp it up. But there are only three manufacturers. If there's any environmental disaster, that might wipe out HRIG, if there's a shortage of the vaccine.

There have been two shortages of HRIG in the United States in the past several decades where they had to decide who would get the HRIG and who wouldn't because there wasn't enough for everyone who wanted it. So the shortage I think in the United States is the biggest issue.

Globally, the idea is that it would cost less, and I think there are ways to manufacturer the monoclonal antibody cocktails so that the cold storage wouldn't be as much of an issue. I'm not sure if they are manufacturing it that way, but I think it would be possible to manufacturer it that

way.

DR. BELL: I don't know that I can answer that, but I'd be curious as to Dr. Harrist's perspective working in the U.S. and the public health arena, what does she see as some of the problems with HRIG in her area.

DR. HARRIST: Thank you, Dr. Bell. I wasn't working during the times of the shortages, but that would certainly have been a very difficult public health problem. As the Department of Health, all animal bites are reported to us, so we give recommendations in terms of post-exposure prophylaxis for all of those people.

I think if there were a product that did cost less, that would be a benefit to patients. Some of these series can cost thousands of dollars, and it really varies how much patients are charged. We definitely have had patients who have an exposure -- and we say, well we don't know if that animal was rabid or not, but we do recommend you get post-exposure prophylaxis, and it's going to cost you $10,000 -- say I need to think about that.

That's a real -- it can be a barrier.

I do think some of the storage requirement -- I mean, culturing to cold chain is not a problem in Wyoming, but the rural nature of our state can be in that some facilities might not stock it because they may not ever see a patient with it, but then they may see 10 come along because of a mass bat exposure, and they don't have it to give, and that has happened in Wyoming. So I think a product that is cheaper and has a longer shelf life would be beneficial.

DR. BELL: So you mentioned it might cost a patient thousands of dollars. Are they asked to pay in the United States, then?

DR. HARRIST: Yes. If they don't have insurance, the patients can be responsible for that. We as a health department used to stock it and give it in those situations. We lost the funding for that, and also a lot of ours would expire before we could give it out anyway, so we stopped doing that.

DR. BELL: That's news to me, so you've lost

the funding to be able to do it, and at one point in time you were able to do it?

DR. HARRIST: Yes.

DR. BADEN: Dr. Swaminathan, do you have a follow-on to your follow-on?

DR. SWAMINATHAN: So I'm a little confused about this continuing discussion of cost. Are we or are we not supposed to consider that this might actually be cheaper to the end user? The second question is, is it a fact that this will have a longer half-life and will pose less obstacles, or is that a hope that that might be achieved?

DR. TROY: So we're not talking about one particular product; we're talking about any possible monoclonal antibody cocktail. It is possible that they could be made in such a way that they would have a longer half-life, but I don't know if -- or shelf life, excuse me, I don't mean half-life. But we can't speak for certain for each one that's developed.

With costs, again, I know the monoclonal antibody in India, they're having a deal with the

government where they're bringing down the price to be comparable to ERIG and less than HRIG, but there's no guarantee how much these will be sold for. We hope that it will be sold for less than HRIG.

DR. BELL: The ballpark is like $3 for ERIG versus $300 for HRIG monoclonal antibody. At one point in time, it was a little bit more expensive, the ERIG, but obviously, even in this country, the pharmaceutical companies sometimes dictate what the cost of products will be, not the FDA or what we can do.

DR. BADEN: Dr. Brown?

DR. BROWN: I'm from the public health sector. I just wanted to second everything that Dr. Harrist said. But then it occurred to me that there could be another potential benefit, but I guess sort of a question.

HRIG, sometimes the problem is that the volume that needs to be injected into a particular area is a real barrier because there's not a lot of tissue expansion. Are the mAb products a higher

concentration that would allow for a smaller volume for infiltration?

DR. DEMING: In terms of neutralizing activity, they can be much, much higher in terms of the concentration of that activity.

DR. BELL: Plus you need less product in that area for as much neutralization.

DR. BROWN: So that actually is one significant potential benefit in the U.S., then.

DR. BADEN: And I think the question to us is we're not considering any specific product. It is, is there a pathway, and we're clarifying that there could be some benefit. If there is a pathway, there may be other collateral benefits, and that's up to the cleverness of the developers to take advantage of those potential benefits.

Dr. Follmann, did you have a follow-on? Dr. Ofotokun?

DR. OFOTOKUN: My understanding of the monoclonal antibodies is that most of them are given intravenously, at least from the HIV world. Will that be the case here or we're looking at

intramuscular injection?

DR. TROY: It would be the same as HRIG, which is it's administered in and around the wound.

DR. BADEN: Dr. Moore?

DR. MOORE: I actually wanted to comment on the approach -- is that okay -- that Stephanie Troy presented, or should I wait?

DR. BADEN: I want to welcome Dr. Ellison back to the table and give him an opportunity to participate in the discussion.

DR. ELLISON: I think that another benefit that hasn't been mentioned yet is that HRIG is derived from hyperimmunized people, which inherently there's going to be a lot-to-lot variation. You don't know what vaccine strain the person has been immunized against. We have two that are completely different in the U.S., and I think that a biologic product that's a monoclonal can be more standardized. So you don't have that lot-to-lot variation that you see with immune globulin products from hyperimmunized people.

DR. BADEN: Please mention your name as

well, for the record.

DR. SCOTT: Dorothy Scott, FDA. In terms of lot-to-lot variation, of course there's a minimum specification, but in some cases, there's also a maximum specification because what you don't want to do, obviously, is to, overcome the vaccine effect.

I have read about lot-to-lot variation. We haven't actually seen a great deal of lot-to-lot variation in potency.

DR. ELLISON: So from what I've seen on the package or the actual vials of HRIG myself, they just say greater than or equal to 150 international units per mL.

DR. SCOTT: Right. They don't have --

DR. ELLISON: I don't know the upper limit.

DR. SCOTT: They don't have the less than specification written on the vial.

DR. BADEN: Dr. Moore?

DR. MOORE: I just wanted to address the difference before the break, that the proposed approach includes serological monitoring. I just

wanted to comment that the cutoff of 0.5 is for serum neutralization assays, and that was established at 4 weeks after vaccination. That 0.5 in serum neutralization assays include IgM and IgG, both, where when you're giving monoclonals or HRIG, you're concerned about IgG.

So I would suggest that assays that would measure IgM and IgG, rather than the total, might be useful in those early days to compare HRIG to the monoclonal to see how much IgG in day 1, 3, 7, would be informative for a direct comparison of what's going on. You would also have to compare that to the neutralizing assay, but you would have two different approaches to compare those two different products.

DR. BADEN: I have a follow-on to your question, which is -- and I think the Goldilocks issue has been raised to get the amount of antibody just right during that window period, but not interfere with the vaccine effect that is kinetically delayed.

Given you know the epitope specificity of

the monoclonal, can't you elute off the monoclonal and look at the emergence of the vaccine effect, to be able to deal with this confounding issue?

DR. BELL: One of our thoughts were that we could essentially subtract out the total.

DR. BADEN: There are two ways to subtract out in that you can do parallel groups with different treatments and subtract out. But can you, in the protagonist who receives both the monoclonal and the vaccine, in the serum of that individual, elute out the epitope of the monoclonal then determining the emergence of the other antibodies not related to the epitope specificity, so you can actually determine when the vaccine response is occurring?

DR. DEMING: So you might lose those components of the polyclonal by targeting the same epitope, potentially. Another way of doing it is instead of using one of the standard laboratory strains like CVS-11 is to use a variant that you know is resistant to the monoclonal antibody. But I believe it would be feasible if someone would

work out and validate the assays using all of those.

DR. BADEN: Because that's one of the challenges that has to be solved in the human studies in the non-bitten individuals, is one can do the experiments to sort out the interaction between the monoclonal and the vaccine, which has to be Goldilocks, not too much, not too little.

Will you please state your name for the record?

DR. LEVIS: Robin Levis in the Division of Viral Products at CBER. I would say while this is a very critical discussion to have in terms of the interference, the typical vaccine response is so great that that you could actually take quite a bit of hit on interference and still have a very acceptable robust vaccine response. So that's something that needs to be taken into consideration, and there is quite a bit of data to support the efficacy of the vaccine's based on the robust response to the immunization.

DR. BADEN: Of course, that's what needs to

be sorted out so that we have a wide safety window to be able to give the different interventions in unfriendly conditions and not worry about this interference.

DR. LEVIS: Correct, but there would have to be a lot of interference, a lot more than has been seen in the studies presented today, to really have us be concerned about the follow-up response to the vaccine.

DR. BADEN: I see.

Dr. Ellison?

DR. ELLISON: Just a follow-up to that previous question. In people that received pre-exposure prophylaxis, that is the 3 doses of vaccine alone -- and they are exposed some time -- any in their lifetime, HRIG is not indicated. That's an important thing that we haven't discussed yet, is people that are previously vaccinated and are exposed with a known exposure do not receive HRIG. They just get 2 doses of vaccines as post-exposure.

DR. BADEN: Dr. Moore?

DR. MOORE: The IgG response to vaccination usually doesn't show up until maybe day 14, where the measurable response from the passive immunity usually disappears. At that point, I think using the IgG assay could show where the passive immunity ends and where the vaccine immunity starts. So I think it would be still, again, a good way to differentiate, measure, and then compare HRIG to the monoclonal.

DR. BADEN: Thank you. Dr. Swaminathan?

DR. SWAMINATHAN: Just a couple of things. This is a naive question. The vaccine interference phenomenon, is the suppression of the vaccine response limited to the serologic response to the monoclonal antibody epitopes, or does the neutralizing activity of the monoclonal antibody cause a broad suppression of the serologic response to vaccine?

DR. DEMING: Someone correct me if I'm wrong, but I I'm not sure the mechanism has really been worked out to that level of detail, but I

believe the assumption is that you're actually facilitating more rapid clearance of the vaccine, which is a killed virus. So it's actually binding of the monoclonal or the HRIG to the vaccine. So it's giving the immune system less of an opportunity to mount a response to that.

DR. SWAMINATHAN: So then the interference could be fairly complex where you couldn't just sort of look at the differential response to different epitopes to determine whether it was -- you said that creative methods might be needed if the neutralizing titers are greater than 0.5, and these are hypothetical examples. But in the studies, what has the level at, say, day 14 from vaccine alone been with monoclonals?

DR. TROY: It's varied. Now, HRIG tends to be low like the 0.2-0.3, so you can easily distinguish because the vaccine response is so much higher. Some of the monoclonal antibodies have been above the 0.5, and our concern, when I say creative methods, would be that, hypothetically speaking, if the vaccine response was knocked out

and the monoclonal antibody alone got more than 0.5, then a measure at day 14 of 0.5 wouldn't measure that. But there are ways we could detect the vaccine interference in that situation, too, that were in the backgrounder.

DR. BADEN: Dr. Moore?

DR. MOORE: Yes?

DR. BADEN: Do you have a follow-on?

DR. MOORE: It still is significantly lower than the vaccine response.

DR. BADEN: Dr. Harrist?

DR. HARRIST: My question's been answered through the discussion. Thank you.

DR. BADEN: Moving to a different line of questioning, one of the challenges presented earlier has to do with the diversity of the rabies virus that infects humans, and should this be 2 monoclonals, or 3 monoclonals, and which epitopes?

Given the sequences of the known rabies virus and viruses that have infected humans, can you rationally design which monoclonals would have

coverage of the rabies species that infect humans and whether would it be 2 or 3 monoclonals; 2, whether it's epitope 3, epitope 2, or 1, can we rationally design which monoclonals we would want that would have the coverage for the globally circulating rabies virus strains that have been known to infect humans?

DR. DEMING: Sure, provided that you had a panel of viruses that accurately reflected the diversity of circulating strains and assuming that neutralization is all that really matters.

DR. BADEN: Well, what I'm getting at is we do have a panel in that we have strains that are known to have infected humans. And we take the most diverse of those strains, and then we rationally -- I guess what I'm getting at is there so much diversity that you wouldn't be able to get 2 or 3 monoclonals because what's already known is too much diversity, or given what's known, one could imagine a manageable number of monoclonals that would have the desired coverage?

DR. DEMING: I don't believe that it would

necessarily take more than 2 or 3.

DR. BADEN: Dr. Green?

DR. GREEN: That's actually my question, is that we've been proposed 2. We've been told that India approved 2. But we've been shown that the human monoclonal has many epitopes. So I just wondered what is the evidence to suggest that 2 is adequate?

DR. BADEN: Dr. Troy?

DR. TROY: I just want to clarify. India approved 1, so that's one that wouldn't be approved. It's just 1. But they're mainly concerned about the dog strains in India, which there's less variation. And I'm sorry; I missed the rest of the question.

DR. GREEN: It's really a follow-on to Dr. Baden's question. What is the evidence that 2 is adequate as compared to 3, given that human polyclonal antibody has many epitopes covered and so nicely shown in those cartoons that we saw earlier in the morning.

DR. TROY: I can just speak to that they had

a whole working group at the World Health Organization to discuss this, and they came up with 2 because they thought 2 would be adequate, 2 or more. I can't go into more details than that.

DR. BELL: My understanding is there are also manufacturing issues, binding within the two different monoclonals as well. Some companies sometimes do different mixes of monoclonals as well; not one to one, I mean.

DR. BADEN: And there are many challenges with deciding what to go forward with, but it sounds like conceptually in an in vitro bioinformatic way, then with cell culture, we could at least imagine data which says here are 2 or 3 monoclonals that have activity against the known circulating human disease-causing strains.

So at least we could have that background as part of the dossier of evidence that at least is a rational approach.

Dr. Moore?

DR. MOORE: I would agree with what you just said, Dr. Baden. I think there are publications

that have shown that 2 monoclonals have broad coverage over a number of different variants that have been tested in cell culture. But I will mention, in cell culture sometimes it's difficult to make equivalent challenge of those different strains in cell culture, but from the publication, it looks like it's possible to have 2.

DR. BADEN: And that's looking at the most diverse strains. So strains that are most diverse from each other and most difficult to neutralize, one can come up with an approach that in vitro has evidence of activity?

DR. MOORE: Correct. You would look at the monoclonal and you identify which antigenic site that it's directed against, and then you would get a complementary one that's directed against another antigenic site, and then challenge them against the diverse variants that are out there in cell culture.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: Following this theme of diversity, is it typical in the context of the

clinical trial to try to collect the strains where available and then see if certain strains explained failure or to add those strains to the panel of what is tested against that product, recognizing that in many cases you don't get the strain? But a trial of this size, you may get the strain from several cases.

DR. DEMING: I think that we would expect that such analyses would be conducted in the nonclinical neutralization work using variants isolated from a proposed study location prior to conducting any type of efficacy or putting out subjects at risk.

DR. SIBERRY: So that makes sense. I guess I'm asking, and then during the trial, you just abandon all efforts to look at collected strains that occurred in participants?

DR. DEMING: Absolutely not. If there were a failure, we would ask you --

DR. SIBERRY: Yes, failure.

DR. DEMING: -- isolate and characterize a virus from any PEP failures.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Just echoing this point, if you could, in the field trial, you'd want to genotype the failures. The people who died, you try and see what kind of virus they had that's similar or dissimilar to the monoclonal antibodies; and I'm just imagining 6,000-person trials that say if you have two failures that both are similar, that tells you something.

But it would tell you an awful lot more if you could get people who didn't die to genotype their virus and then say, oh yeah; 90 percent of the viruses out there were similar, 10 percent are dissimilar, then you could interpret those two dissimilar deaths in a different light and think, yeah, there's really a problem with coverage.

So to the extent you can measure rabies virus in people who don't die, or in the vector, or whatever, that would be enormously helpful.

DR. DEMING: Yes. It would certainly have to be in the vector rather than in people who don't die. But we would be very interested in any PEP

failures because one possibility is that the barrier to resistance isn't high enough and that you're actually getting escape in vivo. We don't think that would happen just given the way that the virus replicates, but it would be a potential concern if we were to see any --

DR. FOLLMANN: See, you're imagining the virus might mutate in the presence of the monoclonal antibody into an escape person?

DR. DEMING: It might, or there's more heterogeneity within the infecting inoculum than we expect. These RNA viruses are very error prone, so it's at least possible that you might actually have some variant.

DR. BADEN: But I think, Dr. Follmann, you're getting at the monoclonals in HIV where there's a lot of parallels. There it's a chronic viremia, so there's different access to the virus, but there are parallels that should be built upon.

Dr. Clark?

DR. CLARK: In discussing mutations, have viruses been passaged in the presence of cocktails

just to see if they evolve, and what is known about that?

DR. DEMING: We ask them to do that as part of the initial workup on any monoclonal antibody. Individually, it's usually not too difficult to select for a virus with reduced susceptibility. Of course, I would defer to either Drs. Moore or Ellison since they actually do a lot of that work.

DR. MOORE: So I think there have been published studies that showed that if the virus is passed in the presence of monoclonals, they develop escape mutants. That's certainly one way to do it, and it has been done.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: for anybody in the agency, we've talked a lot about the considerations for evaluation of a product that basically is a RIG but produced in a different way, and it is only 2 or potentially more antibodies. To what extent should we be considering the specific nature of the potential candidate product, specifically if it's an Fab fragment versus a fully functional antibody?

And I'm thinking mostly about the specific details of neutralization versus not neutralization, and then in an animal mortality endpoint.

Sorry for the open-ended question, but as I'm processing the conversation so far, we've been thinking about RIG versus something that's basically RIG, but it may very well be that it's not basically RIG. So my general question is to what extent should we be thinking about that, or to what extent would the agency apply the same potential pathway to a different product?

DR. DEMING: Are you questioning the assumption that neutralization is the primary mechanism by which these products work? And that's a fair question. I would point out that at least with some of the ERIG products, none of which are approved in the U.S., some of those actually do involve a purification step where they're purifying Fabs, and those are reported to be as efficacious as HRIG.

So at least we have a little evidence that neutralization would be sufficient.

CAPT BURGESS: But some of the mechanisms underpinning the assays that are used may or may not depend upon functional activity of Fc, is really what I'm getting at.

DR. DEMING: Sure. And we would have to rely on the animal models for that, although there are some caveats with that; are the Fc receptors the same; are they going to interact with the human Fc immunoglobulin as well as they would with murine-bearing in turn.

DR. BADEN: A follow-on?

DR. OFOTOKUN: Just to provide a little more reassurance, if you can, we're talking about prophylaxis, post-exposure prophylaxis, which is different from most of the situation in HIV where we are actually developing monoclonal antibody for treatment of an actively replicating virus.

Do you have examples, other than rabies, where monoclonal antibodies have been used for post-exposure prophylaxis, and how well do they perform?

DR. DEMING: Palivizumab for RSV.

DR. OFOTOKUN: For RSV?

DR. DEMING: That springs to mind, and that's been used for several decades now.

DR. BADEN: MIG, TIG, yes, there are others.

It is now 11:45. We have many more questions, so those who thought that we would be done quickly given the succinctness and brevity of the presentation --

(Laughter.)

DR. BADEN: -- I apologize. We will break for lunch. We will resume here at 1 o'clock. We will continue to address all of the questions that the committee has prior to engaging the discussion of the questions.

So we will reconvene at 1 o'clock. Please take any belongings that you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you. See you back here at 1 o'clock.

(Whereupon, at 11:45 a.m., a lunch recess

was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

Clarifying Questions (continued)

DR. BADEN: We will resume the advisory committee meeting. Typically, after lunch, we have the open public hearing element of the advisory committee meeting. As there are no speakers -- or there was one speaker, but they weren't able to participate -- we will continue. We'll have the open public hearing portion, no speakers, and we'll move on to continued discussion.

We will continue discussion from the morning session until we've addressed all of the questions committee members have. After that, we will move to the questions that have been posed to the committee, which includes some more discussion elements. And the intent is to build upon the discussion we've been having and to highlight critical elements for the agency to consider as they chart a path forward for new products in this space.

Prior to the lunch break, on the list, Dr. Clark had indicated.

DR. CLARK: [Inaudible - off mic].

DR. BADEN: Excellent. Dr Weina?

DR. WEINA: Okay. I had raised my hand at about 10:30 --

(Laughter.)

DR. WEINA: -- but I do remember what the question was.

As I looked at the material getting ready for the meeting, it appeared to me that the really critical aspects of, for me, what was important was the preclinical work in the animal models and the vaccine interference. All the rest of it can be sorted out one way or another.

One of the things that struck me is that we have a treatment that is so incredibly efficacious already, or a post-exposure prophylaxis that's so incredibly efficacious already, how do we figure out what's going on with this? What struck me is that for another disease, we had always used a certain drug to treat leishmaniasis. We had always used a drug, and when that didn't work, we used a fallback drug. And when we went back and said, hey, wait a second, it only looks like this

fallback drug is effective 2 percent of the time -- but when we went back and did that as the primary treatment, it turned out it was actually much more effective than our primary drug.

So my question was the same thing with this. Have we really teased out the three different aspects of the post-exposure prophylaxis in which we've looked at -- how it was presented is 99.9 percent effective. And if we add the rip [ph] -- thank you. Geez, my brain froze there for a second. When we added the RIP to it, we add a tiny little bit more efficacy to it.

But how much is that efficacy really present? In an animal model in which we looked at HRIG alone, given right after the challenge with the rabies and the gastroc, or maybe at time zero, or you give the rabies, and then maybe 6 hours later give the RIG, or 12 hours later or 24 hours later, and then compare that to a monoclonal antibody, either singly or together, have those animal trials been done?

It would seem to me that those would be very

instructive and separated out from the vaccine and see how much is the RIG itself by itself really efficacious. We heard you talk about, yeah, we don't do the wound cleansing because we know how incredibly effective that is by itself. We know the vaccine by itself, how effective that is, but do we know how effective the RIG is by itself, and would it be instructive to compare the RIG in the animal model head to head with the monoclonal antibody at 0, 6, 12, 24, 48, 72 hours after being challenged with rabies?

When I looked through all the literature ahead of time, I tried to scan through it, I could find no trials like that, and I don't know if you know of any that are there.

DR. BADEN: Dr. Moore?

DR. MOORE: From what I know, in the publication, it's mostly those early studies in mice, where they gave just passive immunity to show that it was the neutralizing antibody that was causing clearance. But I don't know if there's been in any other animal model, if it's been done

in the Syrian hamster model at all.

DR. ELLISON: We have done it in the Syrian hamster model at CDC. I don't know if it's been published yet, but yes, passive immunizations and RIG does prevent rabies when given post-exposure alone.

DR. BADEN: And in those models, it's injected into the lesion or how is it given?

DR. ELLISON: RIG's administered into the site of exposure. So the same leg that the challenge occurred in the, the RIG is administered and the vaccine's administered in the other leg.

DR. WEINA: And is that uniformly like 99 percent, or is it 75 percent?

DR. ELLISON: I don't know the number straight off
the top of my head, but it is substantially effective, approaching 100 percent.

DR. DEMING: Just to point out in that model -- and please correct me if I'm wrong -- vaccine contributes next to nothing, so you're effectively just doing the --

DR. DEMING: Vaccine contributes very little, if anything, to protection, in the hamster model.

DR. BADEN: In that model.

DR. DEMING: In that model.

DR. BADEN: Dr. Green? Dr. Follmann?

DR. FOLLMANN: Your question was my question also earlier.

DR. BADEN: But then I have more questions that several are going to ask, but I will move forward. This is a question to the agency, Dr. Bell or Dr. Troy. One of the challenges with mortality or failure is the kinetic delay.

How, as you think about the studies to show failure, do you deal with the issue that sometimes rabies may not develop for years after the exposure?

DR. BELL: Good question, but we are thinking we'd want to see at least one year data. It's harder to -- the other thing, logistically -- and I came from clinical practice -- is the retention of people in clinical

trials and those that don't show up. So I think it's harder to do something over 6 years. For the vast majority, it happens in weeks to months, so we think that that might be what we would want to see.

DR. TROY: Someone else can correct me if I'm wrong in this, but I think the cases where it was years after exposure, were people who didn't receive any PEP at all, no wound washing, no vaccine, no anything like that. So I'd expect in these trials where everyone's getting wound washing and vaccine, that if you had any deaths from failure, it should be within the first year.

DR. BADEN: Do you think failure first year, first month, first 2 to 3 months? As one thinks about the trial design, when you anticipate 99 percent of the failures to occur would be a window of observation.

DR. TROY: I think it depends on where the bite is because I think a lot of the variety is if the bite's, again, close to the head, we would expect the failure to come a little early. If the bite was further away, it might be later. So I

think it'd be hard to guess that beforehand. But I think in the vaccine trials they've done, that they have usually followed for a year afterwards.

DR. BADEN: I guess the tip of the big toe would be the longest trends of time.

Dr. Green?

DR. GREEN: As Dr. Baden predicted, his questions would -- it wasn't quite my question, but I have a follow-on to it. So it really is -- and maybe it's a comment more than a question, but just wondering if there's a way to build in. So if you have active follow-up in the study for a year, is there a way to -- at least if subjects in the study die within several years of the study, after or beyond that first year, a way follow?

The reason I think about this is that I chaired the disease transmission advisory committee at UNOS when the human-to-human transmission occurred, and that recipient died somewhere around 18 months after getting an organ transplant from an index case or a donor that died of rabies. We were all fascinated and couldn't understand why an

immune-suppressed patient would have such a lag time, and people thought it might be because it was raccoon rabies and not bat rabies and going on.

But it does raise the question that there could be a late failure signal, that of course you may not be able to invest the money or infrastructure to actively follow all subjects, but at least to have something planned if somebody dies with an X number of years without an obvious explanation. And the donor in that case was not thought to have died of rabies. It was only in retrospect that they confirmed it.

DR. BELL: Thanks for sharing that information, but as you mentioned, we'd have to review the protocol and think about things. We don't have answers right now for a specific product.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: I think on the other side of thinking about, unfortunately, a rare event like mortality as an endpoint in the study designs is if we're thinking in 750 participants, that there may

be hopefully no more than one death, how do you account for a plan for the possibility, stochastic possibility, that that one death shows up early, and would one early death mean you were done? Yet, it could just be bad luck.

Maybe someone with statistical expertise can help us think about how we also plan for what would be unlucky possibility that one early death could really throw off our perception of the product.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Yes. I'll try to answer that. This is really hard in this situation. Usually we have boundaries and look after a certain number of events or certain number of people who've been evaluated. This is so rare, I think my impressions were thinking maybe 1 or 2 cases, or 3, would be a real warning signal. And if it happened in that first hundred, that would be game over, really. And if it's bad luck, well, you can't protect yourself completely against bad luck, I guess.

So I think if we do a 6,000-person study and

if there's a small number of deaths -- I don't know the number, 4 or 3 -- it would be I think hard to go forward with it.

DR. BADEN: I think that this is why DSMBs have such an impossible job and need all of our praise, because you're right. If there were to be 1 death in 750, and it happened to be number 7, you don't know what's going to happen in the next 743. It's an impossibility. But that is why there are statistical boundaries and DSMBs to try and weigh it, and my sympathies go to them because it's inevitable that that will occur in these studies.

DR. FOLLMANN: Right. And if you have a first death in a hundred, you have a very high estimate of mortality. That's a fair estimate, 1 out of a hundred. It's just not acceptable I think for this setting.

DR. BADEN: But will also speak to the kind of mortality they capture because the death might be a motor vehicle accident.

DR. FOLLMANN: Right. I'm thinking this is like --

DR. BADEN: -- if the person is goofy when they're driving, which is how some previous cases have occurred. So how one tracks -- because there will be traumatic and other deaths unrelated to this study at all, but one will have to ask the question could something about the disease have precipitated what appears to be an unrelated event. But that's baked into the study design and the follow-up.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: This isn't really a follow-up question. Is that okay?

DR. BADEN: Go ahead.

DR. SWAMINATHAN: Just in thinking about the risk of death, it's been discussed that there are various factors that make it a higher risk exposures such as proximity of the bite to the CNS, but that's the first one, the most obvious one that comes to mind. With all the difficulties of having the power just to get 600 or 6,000 people, you are not going to then certainly have the power to stratify the exposed into higher risk groups. Even

with HRIG, in a worst-case scenario, you get bitten in the head by a rabid wolf, you have an 8 percent chance of death.

I'm just concerned that these things could look equal in neutralizing ability in vitro and animal challenge studies and look good in the larger clinical trial after it was done. But it wouldn't rule out the possibility that in a high-risk exposure, that they would not be equally efficacious.

DR. BELL: You're right. And I bring back Dr. Troy's graph where the uncertainty amongst that 99 percent with the yellow bars is there. Unfortunately, that's inherent in this disease process. The inoculum of the virus isn't always known and the type of bite. There's just a lot of variability in a lot of things we probably wouldn't be able to quantify with this condition.

DR. BADEN: Dr. Clark?

DR. TROY: Just one other follow-up on that, which is that, unfortunately, this is one of the situations that the population that'd be most

informative to test this on, the really high-risk bites, will be the ones that ethically would be the hardest to test on.

DR. BADEN: Dr. Clark?

DR. CLARK: I was just going to say something similar, that you think you would focus at first on lower-risk bites and enroll I don't know how many of those. But yes, that may not be as informative either, so it's a difficult issue.

DR. BADEN: Dr. Green, you have a follow-on? No?

Dr. Follmann?

DR. FOLLMANN: Earlier I said 3 or 4 deaths might be too much. I don't know that's necessarily true. I'd want to study that more. What I wanted to get to your point is that for any deaths that occurred, the circumstances of the death, the location of the bite, the exposure, how much of the wound washing did the vaccine take properly as well, would be all extremely important. There would have to be an intensive investigation of the circumstances of each death to try to sort out what

effect the antibody had or didn't have.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: I just wonder if given all the difficulties with drawing conclusions because of logistical difficulties of these studies and also not really knowing -- even though the correlate with neutralization activity is there, we don't really know all the ins and outs of how the passive immunization prevents disease.

Would we ever feel comfortable generalizing the results of a large study where the vast majority, even though they may be group 3 or whatever, of exposures are not these very high risk exposures, and whether we would ever feel comfortable generalizing the use to the high-risk cases?

DR. BADEN: I don't know if Dr. Deming, Moore, or Ellison want to comment.

DR. MOORE: I just wanted to comment on animal studies, licensed animal vaccines, rabies vaccines. They do a pretty severe challenge, which is injection in the cranium, and they do serology

also. So it's known that for animals that have -- the higher neutralizing antibody they have up to a certain point, the greater probability they have of surviving. So we do know that in animal studies, but we also know that after a year or three years, there are animals that don't have detectable neutralizing antibody and serology that will survive.

One publication that I was involved in looking at wild animals, we saw that if we measured the neutralizing antibody at day 28, it was more predictive of survival than measuring the antibody right before challenge. So we do have correlate of protection. It's just like when are you going to measure it and what level it is. So we do have it in animal models.

DR. BADEN: I have no follow-ons. I still have more on my list. We have focused on the Ig component. What about the vaccine component? Because there's more than one vaccine that's approved and used. Does that matter which rabies vaccine's being used in combination or is that a

neutralized factor?

DR. TROY: I might defer to Robin and Dot for this one, but I think the approved vaccines in the United States are trusted equally.

DR. BADEN: And we don't think there'd be any interaction with different monoclonals and the different vaccines that might be deployed in conjunction.

DR. TROY: Not that I know of, but there'd be a greater risk with one vaccine over the other because it's a different killed virus.

DR. BADEN: Yes. If there is this inhibition element, could that inhibition be differential depending on which vaccine product you're using, and how has that been assessed to make sure that that concern is a phantom concern?

DR. TROY: That's a very good question. I would think these studies in the healthy subjects would be very important for this, and maybe they could use both the different types of licensed vaccines when they do the vaccine interference studies in the healthy volunteers.

DR. BADEN: Because that would be both the two U.S. licensed ones, but I am not aware of the vaccines used in India or elsewhere because you would want to understand the interaction with what vaccines are being used in the community. I would presume there's none, but I don't like presuming. It's where there are data that can reassure us that this type of concern's a phantom, and it's just knowing where it's deployed.

The washing, the Ig, and the vaccine are the elements and to make sure they truly are independent and don't interfere with each other. I think the vaccine, presumably, there's a limited number of vaccines used globally. Presumably, there would be no issue, but that would be something to think about as another modifiable factor. I don't know if any of our virologists have any thoughts on that it shouldn't be an issue.

DR. LEVIS: This is Robin Levis from the Division of Viral Products at CBER. Certainly, we can't imagine it would be an issue with the two vaccines licensed in the U.S. Globally, there are

a variety of different strains that make up the vaccine, so it is an important thing to take into consideration the different strains that are used; although -- and anybody can correct me if they have more knowledge of this -- despite the strain differences in the vaccines, they've been uniformly successful at preventing disease, so the coverage has been good.

The other thing to take into consideration with regard to the vaccines is route and dosage of administration because there's a very wide variety globally, whether it's intradermal, multiple shots, on the same time, the number of doses. So that's something that also needs to be considered in the package.

DR. BADEN: Dr. Green?

DR. GREEN: So this is a direct follow-on. Would there be a reason in the animal models to do the combinations with the varying vaccines from outside of the United States? And in particular, since we're going to do these studies primarily outside of the United States, the questions of

interaction of the monoclonal with vaccine take and durability, although I guess it's more about vaccine take because durability may not be that important, seems like it needs to be addressed unless you're going to mandate and study that they use a limited number of vaccines or a U.S. vaccine.

But I would think you could do in an animal model, it's just a matter of how much money you want to spend, get the vaccines from the major countries that are in play like India or what have you, and just assess that same question. Again, it's the notion that we're doing studies; that we're going to give it potential and approval in the United States. We already said it's going to be against a population that has dog rabies already. And now they've got dog rabies and a non-U.S. vaccine with this, so the ability to extrapolate just gets a little bit more unclear.

DR. DEMING: Sure, those studies could be done in animals, but they can also just be done in healthy volunteer studies as well.

DR. BADEN: Dealer's choice. Dr

Swaminathan?

DR. SWAMINATHAN: As I understand it, the studies would be done, as you say, in a location where the infecting strains are different from the U.S., and we've been talking about the strain diversity and ways to address that so that it could be potentially applicable to exposures in the U.S. But my question has to do with not just the difference in the strains that circulate in bats in the U.S.

This is where I'd like some clarification from rabies experts because we consider, even inapparent contact with bats, to be a category 3 exposure. Like I said, I've taken care of one patient with rabies, so I guess that makes me an expert, but not really. So I would like to know whether the pathophysiology of a bad exposure, is there something fundamentally different about that? And if there is, there may be more to the problem of generalizing from countries where the exposures are all from dog bites, besides just strain differences that can be addressed in vitro.

So do we need to be concerned that that also would somehow have to be addressed?

DR. TROY: Just one comment, in that I think some of the issues between the dog bite and bat bite would be problems for both HRIG and the monoclonal antibody cocktail, meaning that with a bat exposure like you said, sometimes it's in the parent contact, so where do you inject it? That wouldn't just be for the monoclonal antibody; that would be for HRIG, too. So this is I think a problem for all passive immunization, not just for development of monoclonal antibody cocktail.

DR. SWAMINATHAN: But we feel comfortable that giving HRIG to our bat-exposed patients here works, rightly or wrongly. How do we prove equivalence or noninferiority with something that is not going to be tested in that situation?

DR. BADEN: I think that probably gets to the study design, is that the applicant will have to say here's the product and here's the kind of study, and then there will be debate as to where do you start and how do you escalate. But I

suspect that may have nuance depending on the applicant and what the product characteristics are and be part of the study, but I don't know if the agency has comments.

Dr. Ofotokun, and then we'll come back.

DR. OFOTOKUN: I just wanted to follow up on that also. We've talked about strains from India, and also the rabies issue in Africa and in Latin America. I just wanted someone to comment on whether there are differences in strain from those parts of the world, Latin America. A lot of Americans that come home with bites are usually coming from either Latin America or Africa.

Can you comment?

DR. BADEN: Dr. Ellison? Dr. Ellison has a comment. Thank you for facilitating the tracking of the commentary.

DR. ELLISON: Just a few comments about that. Yes, in the old world, Africa, Asia, the primary reservoirs, the dog, phylogenetically, there are very little clades -- there are some variations, but there's not much as compared with

the diversity we see in the Americas. In Latin America, vampire bat rabies is a big problem, but also their epidemiology is different. They actually prey on humans if there are animals unavailable. We see outbreaks there all the time.

To follow up on Dr. Swaminathan's comment, in the United States, yes, the majority of human rabies is associated with bats, but they're also associated with what we ought to call cryptic exposure; the exposure is unrecognized. And we actually don't even know what variant it is until autopsy post-mortem, then we're able to sequence it and find out.

They probably would have got post-exposure prophylaxis had they have known it. Typically, when taking history with the family, they say, "Oh yeah, we had bats in our attic," or "Oh, we had a bat in our room two months ago and didn't think about it, and threw it out." So I think also the nature of exposure is different.

Just in terms of the U.S., we've had maybe 4 human cases over the past 2 years, but 2 of them

was dog variant, but they were associated with U.S. travelers. One last year from India was bitten by a dog and the other one was a soldier from Afghanistan, also bitten by a dog.

DR. BADEN: And the other two were bat?

DR. ELLISON: Bat. We had a raccoon case late last year.

DR. BADEN: And then I see your card is up. Do you have a question?

DR. ELLISON: It was about the cryptic exposure.

DR. BADEN: In 2017, KEDRAB was approved. Can you expound a little bit on the basis of that approval? Because presumably, that had some of the -- even though it is an HRIG, it's still is a newcomer. What were the key elements of that approval process that can help us as we think about an approval path?

DR. TROY: I can start, but Dot can also jump in because she was more involved in the approval. But the approval for KEDRAB was primarily based on the serologic endpoints. I

think it was 160 -- 150 healthy volunteers. However, it was a unique situation because it was already approved in multiple other countries. So they came in with data from other countries, that about 250,000 people had already received it, and there had not been reports of any failures. So it was based on the serologic measures, but it was heavily supported by postmarketing data from other countries.

DR. BADEN: What were the serologic measures?

DR. TROY: The primary endpoint was, I believe, the day 14, the late RVNAs levels.

DR. BELL: So they did use late RVNA levels, and apparently they collaborated with the CDC in terms of discussion and some flaws in using day 14 endpoints.

DR. GREEN: Just to clarify on that, that endpoint that they're looking at, that's using the new monoclonal -- or the new polyclonal in combination with vaccine. And if they're looking at 14 days, they're looking at a composite antibody

total, correct?

DR. TROY: Yes.

DR. GREEN: Thank you.

DR. SCOTT: Dorothy Scott, CBER, FDA, Division of Plasma Protein Therapeutics. Yes, that is the case. The day 14 was I believe their primary endpoint, however, they've done pharmacokinetics throughout the time period after giving the HRIG, and all the way through after having given vaccine.

So we did have data from those initial days where you expect RIG to work, HRIG to work, and that was also compared to one of the licensed products and found to be acceptable. But nevertheless, it's still a serologic endpoint supported by a very vast number of doses given without reports in a fairly rigorous system. I think it was in Israel, and it's likely they would have counted a rabies case.

DR. BADEN: When you say compared, the serologic profile was compared to a licensed product?

DR. SCOTT: Yes, to a licensed HRIG.

DR. BADEN: Okay. So it was the --

DR. SCOTT: We have Imogam and HyperRAB.

DR. BADEN: And it had a similar serologic profile?

DR. SCOTT: Yes.

DR. BADEN: So one can consider that as a ruler or a benchmark to be compared --

DR. SCOTT: A surrogate marker, basically, surrogate type marker.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: It's not a --

DR. BADEN: I think we're in the -- if anyone has questions, please come to the plate.

DR. FOLLMANN: That's my green light? All right. I want to talk a little more about the proposed design for the pre-licensure study, which was mentioned, that maybe 750 people would get the monoclonal antibody. And there was discussion in the materials -- though I don't think it was presented today -- about having a 3 to 1 randomization, so there'd be 750 people getting the

mAb, and then 250 people I guess getting HRIG.

Usually randomization is equal, and I'd like a little more discussion about why you want to do 3 to 1 randomization or favor the mAb arm in terms of people.

DR. TROY: For the pre-approval study, we're actually thinking more like 1-to-1 randomization. It was the postmarketing study with the 6,000 that we're thinking the disproportionate randomization with 6 to 1 or 3 to 1. And that was more just because if we're already requiring 6,000 subjects to receive the mAb cocktail, that's going to be hard enough.

DR. FOLLMANN: I see. Thank you. So just to clarify, you do 1 to 1 in the initial one, maybe seven 750/750 --

DR. TROY: Yes.

DR. FOLLMANN: -- or something like that. And then in the other one, it would be 6,000 get mAb and maybe 2,000 get the HRIG?

DR. TROY: That was our thought, that we didn't clearly define it.

DR. FOLLMANN: Okay. And you wanted us to comment on that. It's interesting in a way because usually when you randomize, there's a comparison between the two randomized arms. The way this is being laid out is there's not really a plan for a formal comparison. You're not powering it for noninferiority; you're not powering it for superiority.

So I view this as, say with the initial one where you do 750, like at 750 and 750, if you see what 0 out of 750, in the mAb arm, that would be a green light. Then is there a formal or what's the informal purpose of the 750 with the HRIG?

DR. TROY: Safety, the main thing --

(Crosstalk.)

DR. FOLLMANN So it would it be more of a safety comparison, not looking at mortality but just to --

DR. TROY: Yes. There would be comparisons with serologic endpoints, too, but you would pick that number for that.

DR. FOLLMANN: Okay. And the same thing I

guess wouldn't be true for the 6,000-person study; that would also involve a safety comparison?

DR. TROY: Yes, that is correct.

DR. FOLLMANN: Thanks.

DR. BADEN: Please, Dr. Siberry?

DR. SIBERRY: That seems like a big study for a comparison of safety when I'm not sure what the exact safety concerns would be with that monoclonal product. And the serologic endpoints, again, it's hard to understand why you'd need 750 in each arm to get the information you'd need. That just sounds much bigger than what I'm used to thinking about for short-term safety events and for serologic endpoint comparison.

DR. FOLLMANN: I think the 750 is also important for mortality. If you see 3, 4, or 5, or some number that fail in the mAb arm and not in the other arm, that would be important. You need some kind of assurance. You need a certain number that gives you some comfort about mortality; maybe not definitive but enough to allow you to disseminate it and then allow for the postmarketing thing. So

I view the 750 as important for mortality as well as the serologic endpoints, which you get with a lot less. I agree.

DR. SIBERRY: I just think we should separate them, the objectives. If there's short term safety and serologic objectives that require smaller numbers, that should be thought about what you'd need for that. If you tell me that you'll get meaningful information about a mortality difference by having 750 per arm, and you're the expert, help me understand. But again, I think we'd be looking for the number of deaths in those 750 mAb recipients almost regardless of what happened in the 750 other recipients.

I think it's worth some more detailed discussion about those three sets of objectives: short-term safety, serologic endpoints, and mortality, and whether the 750 is needed for each of those.

DR. FOLLMANN: Right. I think what they could do is they would do power calculations, presumably, per serological endpoints, and a lot

less than 750 might be able to achieve what they want. For safety, I guess they could do similar calculations, but I would think the bigger the safety database, the better. The mortality is just that if you have 0 to 750, survival is 99.5 percent or better, which is a nice number to get a green light to study it in a postmarketing environment.

So it's always sort of a trade off, how much do you want in the initial phase before you go on to the next phase, and they're anchoring it to the nice number of 99.5, I think.

DR. BADEN: Debate is good.

DR. SIBERRY: I hope it's coming through as discussion more than debate.

DR. FOLLMANN: Oh, yeah.

DR. SIBERRY: I think the way you've described it, though, do you need 2 arms to be able to conclude that 0 out of 750 gives you confidence that the mortality risk is low?

DR. FOLLMANN: I think you need another randomized arm to just ensure the attack rate is more or less what you want. It could be you get a

lot of head bites and whatnot, and the mortality is quite large in the mAb arm, and it might be even larger in the HRIG arm. It's a reference. I view it as kind of a reference control to guard against that.

You earlier talked about bad luck, 1 out of 100. Without a control group, you're even more in the dark about interpreting it, I would say. There might also be benefits of here's a study where we're giving RIG or mAb in a blinded fashion that might be a little more palatable than a 1-arm study with an investigational agent.

DR. SIBERRY: This is, again, helpful. Again, the expectation is zero deaths in both of these arms.

DR. FOLLMANN: Right.

DR. SIBERRY: So it's a little different from a trial design when you're expecting say 10 to 20 deaths per arm, and you really want to understand this. Again, you have more expertise in this, but when the expectation is zero in each of these arms, I'm not sure how much more you're

gaining by having --

DR. FOLLMANN: No, right. And that was related to the question I had earlier; what's the justification for this without a formal comparison? I think it's like an informal canary in the coal mine or an informal reference that nothing's seriously amiss, and it can help you interpret things. I think the study is much stronger with that, even if there's not a formal powered comparison.

DR. BADEN: There are at least 3 or 4 follow-ons. I think Dr. Baker has first dibs on a follow-on or is it a different line?

DR. BAKER: [Inaudible - off mic].

DR. BADEN: Okay. Then Dr. Kartsonis?

DR. KARTSONIS: I pretty much just wanted to reiterate what Dean was saying. I think there is value, obviously, in having a placebo component, and that 750 to be able to provide --

DR. BADEN: Comparator.

DR. KARTSONIS: -- comparator. I'm sorry, a comparator, not a placebo, for that particular arm.

I think the pharmaceutical company would want it as well, because I don't think they really want to be putting forward something that could have potentially shown that there was a potential difference. But I think it also helps the pharmaceutical company in many ways as well, that if there was 1 death in both of them, then that helps both the agency as well as the pharmaceutical company on helping to decide what's the next path forward.

So I think it does make a lot of sense. But just to reiterate what George was saying, is that at the end of the day, we're assuming zero deaths in both arms before we would move forward into post approval of then postmarketing studies.

DR. BADEN: Dr. Weina?

DR. WEINA: I just wanted to jump in on that because one of the things that I ran across as I was looking through the literature was the Chinese study with all of the people that they -- tremendous numbers of cases. And they looked at, know, although the vast majority of them

were successful, the tremendous variability in when people came for care to actually get treated and how much variability there was in the wound cleansing prior to what's going on.

So there may be just a tremendous amount of pure dumb luck as to how many people actually survive or how many may end up with it. So a comparator arm becomes really critically important from the perspective of saying, hey, we're treating them the same, but also to look at every single death in depth ahead of time, as was already mentioned, so that you can kind of say, yeah, these guys came in a week after or 2 weeks after the bite occurred.

The chances are that this may not do anything at all, and maybe the person shouldn't even be enrolled, or having the trial set up with really tight parameters as to -- but then enrollment's really going to suffer a lot because I couldn't believe the amount of variability that they reported in these studies out of China with very large numbers of individuals, so it's a

double-edge sword.

DR. BADEN: Dr. Swaminathan, a follow-on?

DR. SWAMINATHAN: Just to get back to the utility of this first group, or groups, for serologic data, it seems like those graphs, those hypothetical graphs, we would have real graphs in humans, particularly with respect to the comparison of interference with HRIG versus the monoclonal. It seems that that would be very important just to guide further development and understanding of this whole area.

Given that we heard that there can be significant inter-subject variability in vaccine response, how would you calculate -- it was implied that the number would not be great, large, to obtain the serologic data, but it might be quite large if there's significant inter-subject variability in vaccine response. So if you want to get those nice curves --

DR. FOLLMANN: Yes. To me, that's sort of a controlled experiment you can do. You can do power calculations. You can look at variation in that

and study it more. So that's all knowable in my mind.

DR. SWAMINATHAN: But that might be a reason that you might need a larger group, even for the serologic.

DR. FOLLMANN: Yes, you might. But I think, just playing this out, you would get a representative group, more or less, see if there's a lot of variation or not, and maybe there's a certain subgroup or a certain category of person that has a really bad response, and then you would study them further. But this is all knowable through experiments that aren't done in the field, really, done at the clinic.

We have a lot of control over that. We'd want to have comfort that vaccine interference is not an issue and that serologies are similar for the broad range of people, I guess, that would be in this study. If we need to study some groups or subgroups specifically, we would do that, or should do that.

DR. BADEN: I think at this point we're

still focusing on extracting as much as we can out of the presenters and the discussants. As we get to the questions we will need to probe many of these discussion points. I just want to make sure we leverage our presenters fully.

I think, Dr. Baker, you had a comment/question, maybe more than one.

DR. BAKER: Yes, a question regarding some of the variability issues that have been raised. Have there been any published guidelines regarding the PEP administration promptly and correctly?

DR. TROY: That's the issue. They all say prompt, but they don't give time lines. The only time line they give is if RIG is delayed and they start the vaccination series, then after 7 days after starting the vaccination series, they don't think the RIG is very useful anymore because the vaccine-induced antibodies hopefully will have kicked in.

So there's that timeline that's given. The general consensus is that you should get it at any time point. You want to do it as soon as possible,

but if a week after someone got bitten by an animal that might be rabid and they come to the doctor, they should still get the prophylaxis then, or a month later.

DR. BAKER: Another question regarding pediatric studies, there's a comment here that the trials should be expanded to pediatric subjects, but is there any consideration to moving away from should to must?

DR. TROY: That's been a topic of debate. Given how many people who present for PEP are children, I think must might be a good idea, but that's definitely been something we've talked about.

What do you think?

DR. BAKER: Well, I think, yes, animals and children. I haven't seen the data here about bites in children except for the one case in Iran, but I'm assuming there must be some data there, looking at how many bites do occur in children. Then I would assume there would be dosage issues that are different, but that's an assumption.

Also, in terms of feasibility of trials, if you need a family to be present for a length of time for the administration of PEP, consideration for support for that family's presence in the clinic setting for the proper administration during that course.

DR. BELL: You're going to be asked the question of how to label it. Another way to get around that is to label it for adults, but its use would be crucial for kids as well. I'm just bringing that out there because that will be one of the questions.

DR. BADEN: I thought earlier one of the presentations said about half of the doses in the U.S. were given to children, or maybe I'm misremembering, or a substantial number.

DR. TROY: I think substantial. I think it's half worldwide.

DR. BADEN: But a substantial number is given to the tune of tens of thousands in the U.S. and millions globally.

DR. TROY: Yes, it's at least 50 percent.

DR. BADEN: Yes. So it is a highly relevant and salient population.

Dr. Clark?

DR. CLARK: I had a question about children as well. Would that mean that they would have to participate in the volunteer experiments to assess antibodies, or would you extrapolate after having adult data and just enroll them in trials after they were exposed?

DR. MURRAY: I think we'd have to have the potential of some benefit. Usually, we don't do drug interaction studies in children and serologic studies, so I think they would have to have some potential of benefit. So I think you could probably only do studies in children in exposed individuals by the rules, the regulatory rules, and ethics rules, and all that, prospect of benefit.

DR. TROY: And this is where it would also be a very good idea to do it in places where RIG's not available --

MALE VOICE: I'm sorry. Could you repeat that?

DR. TROY: This would also support doing this in places where RIG is not available.

DR. BADEN: Dr. Farley?

DR. FARLEY: Just some information in terms of the regulatory framework. As Dr. Murray pointed out for children, there would need to be some prospect of benefit to the individual established, and that would be a matter of discussion in the course of the program. But likely, the participation of children would be at the level of rabies-exposed children because that would be the group that would be likely to benefit.

Sponsors are required early on in the course of their development, by the end of phase 2 now, to submit a pediatric study plan in the United States, so a lot of the discussions in line with some of the concerns that you've raised would be brought up by the agency at that time with the sponsor.

DR. BADEN: Dr. Baker? Dr. Baker, did you have a follow-on? Dr. Follmann?

DR. FOLLMANN: As I was listening today, I was wondering how -- in the studies, you want to

enroll people who've had exposure, but how do you know they'd been exposed, basically? Like if a dog bites them, the dog is sacrificed and known to be rabid, that's one thing. If there's a bat in the attic that the dog drags out, that's very different.

These studies are sort of predicated on the idea that there are 6,000 who had meaningful exposures, and I just wonder or worry about how that might be implemented in the field, especially with pressures to enroll and maybe encouraging people to come in with potential bat exposures. I guess it's just a comment that in the design of the study, I guess you'd have to have strict criteria for what exposure meant, and you'd want, as best you could, a meaningful exposure to be defined.

DR. BELL: It's hard to predict what type of exposures were to happen, but one idea would be in the postmarketing setting to ask for less numbers, if you get the more serious exposures, the head and neck, or the confirmed exposures. And that's just theory; that's nothing we're saying right now.

DR. BADEN: But does the category 3 try to get at that?

DR. BELL: Well, I guess category 3 to the head with a known dog and a kid is a little different. If it was enriched somehow for that population, it might give us more assurance.

DR. FOLLMANN: Could you get a category 3, like a dog bite to the head, and the dog goes away, and you don't know if it's rabid or not, and that would be category 3? Because it's odd for a dog to bite you in the head, I guess.

DR. TROY: A dog bite to the finger, where the dog went away, could be a category 3. So category 3 is usually just a transdermal bite from an animal that's possibly rabid.

DR. FOLLMANN: Right. So there is some uncertainty about whether exposure was meaningful or not --

DR. TROY: Yes.

DR. FOLLMANN: -- and that's just the state of affairs.

DR. BELL: Obviously, the more proof would

be if you were to have a rabid exposure, God forbid, and the high likelihood or location to have clinical disease, but you can't control that.

DR. BADEN: Dr. Green?

DR. GREEN: This is a follow-on to the question when we're looking at if the -- I guess the word "kinetics" might be the best of using a monoclonal in a child versus an adult was different. And I wonder if there's any known examples from other monoclonals that have been approved that have been used in kids and adults that demonstrate that they have either different requirements of milligram per kilogram infusion and/or kinetics of the product when given.

I think they're probably more therapeutic rather than preventive monoclonals, like we don't have a monoclonal for chicken pox. VariZIG is a polyclonal, et cetera, but there are monoclonals that are used in adults and kids. So there might be some at least ability to see if there are differences that you could predict that might need to be taken into consideration.

DR. BELL: It's a good suggestion. Off the top of my head, I'm not aware of any differences. I just don't know. I can't say there aren't any differences.

DR. BADEN: I think Dr. Ellison --

DR. ELLISON: Going back to the meaningful exposure example, it's important, when developing risk assessments for advising people on post-exposure prophylaxis, was it a provoked bite or was it an unprovoked bite? Being the unprovoked bite, it's more likely to be rabid.

Also, the geography of the area, half of the United States doesn't have a terrestrial reservoir, so if you're bitten by a skunk in Washington, or you're bitten by a skunk in Pennsylvania, there's different likelihood; although it is possible that a bat variant could spill over into a skunk, and the skunk bites the person. But part of the risk assessment is taking into effect all the factors.

DR. BADEN: Very challenging for study design.

Dr. Swaminathan?

DR. SWAMINATHAN: I was just going to ask, in other countries, aren't most of the situations that require PEP and vaccination, passive and active vaccination, aren't most of those unconfirmed? What percentage is actually confirmed elsewhere? Because even in this country, the bat exposures are not confirmed because the offending animal isn't around.

DR. BELL: We had an expert from the Philippines come to our public workshop, and she detailed that the numbers went down significantly. They used to get hundreds; now they get more on the order of 20 per year number, so the number went down substantially.

DR. BADEN: Twenty per year, confirmed.

DR. BELL: That they get the heads.

DR. BADEN: But that means -- the overwhelming vast majority are unconfirmed, which is just the state of affairs.

DR. BELL: And don't quote me on the specifics, but in general, the amount of documented rabies able to get animals to confirm they're rabid

has certainly gone down in her experience, over the course of time, to where now it's very limited to get actual data.

DR. BADEN: Dr. Weina? Oh, I'm sorry. Dr. Moore, and then Dr. Weina.

DR. MOORE: Part of that is getting the animal, but the other part, in many areas of the country where rabies is a big problem, is lack of diagnostics and lack of reagents because it is a neglected disease, so we've got two problems there.

DR. BADEN: Dr. Weina?

DR. WEINA: I was just going to comment on practical experience. I sit on the rabies board for Virginia, and their guidelines are real straightforward. If there's a bite and you can't observe the dog or the animal for 10 days, they get it, period; no if, ands, or buts. They've been exposed.

Given their perspective on it, it is that the uniform fatality rate if they don't get treated is too high a risk based upon the minimal type of intervention that you're going to have to do with

them. So that's basically the guidelines, and you almost have to argue not to when the risk is exceedingly low on a regular assessment. So I think state by state, there's tremendous variability.

DR. BADEN: Any other clarifying questions from committee members?

(No response.)

DR. BADEN: Okay. Any other comments from the agency before we start the discussion of the questions? Please?

DR. SCOTT: Dorothy Scott, FDA, CBER. I'm just getting back to you with some information about stability of HRIG. At least one of the products is stable. The data comes from accelerated stability protocols on a number of HRIG lots at 30 degrees for 3 months and at 25 degrees for 12 months.

So that just gives you an idea, at least, of the HRIG's stability and how it might perform if there was a temperature excursion in tropical places. But the other thing I would say is that

you can make any polyclonal immune globulin more stable simply by lyophilizing it. It will stand up to heat a lot better.

We have some products that have lasted more than 15 years that are lyophilized. This would be the coral snake antivenom, for example, which is used in Florida and hasn't been manufactured for some time, but still is licensed. I imagine the same may be the case for monoclonal antibodies. I just don't know.

Questions to the Committee and Discussion

DR. BADEN: Thank you. We will now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will be using an electronic voting system for this meeting. I'll go through the procedure, and then we will open the discussion. We'll be using the electronic voting system. Once we begin the vote, the buttons will start flashing and will

continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll go around the room, and each individual who voted will state their name and vote in the record. You can also state the reason you voted as you did if you want to. We'll continue in the same manner until all questions have been answered.

Now, this is a bit of an unusual meeting in that there's actually greater interest in the discussion of the challenge before us and before the agency and the community as we try to advance a product in this space. The agency would like us to discuss a little bit of the issues amongst the members, as we've already started to in the clarifying questions, to better illuminate the

challenges and what would be key elements of a path forward. 1 is the preamble to the vote in 2; 3 is the preamble to the vote in 4; and 5 will be the epilogue.

The first question, which really is more of a discussion, is what information is needed to support trials in rabies-exposed individuals? Please discuss any recommendations concerning the data required prior to evaluating a monoclonal antibody cocktail in place of RIG in clinical trials and rabies-exposed subjects?

What will occur when we vote is do we think there's a path forward, and then what would the key elements be to the path forward. But the discussion question on the floor is what is needed to move mAb forward in the context of RIG, and the floor is open to discussion.

Dr. Swaminathan?

DR. SWAMINATHAN: I think the animal challenge studies that support this should have relevance to the strains that circulate in areas where the vaccine might be applied. More than one,

perhaps, animal model might be required so that there's adequate coverage that the disease would be high enough penetrance in the model, so that the vaccine efficacy in that model would be generally applicable to the entire human clinical spectrum for which this product might be used more.

DR. BADEN: Dr. Weina? I think there's a lot of interest, and we'll work our way through everyone.

DR. WEINA: Again, my comments are on the animal challenge studies as well. Just demonstrating survivor benefit, as I've alluded to earlier, I think we really need to focus just on comparing the currently used HRIG with the monoclonal antibody alone, not with the vaccine, in the animal model, looking at mortality but measuring it after the animal has been challenged at time zero, and at time 6, and at time 12, and out several days to kind of get an idea of the comparison of the monoclonal antibody to the HRIG; and if the time period stretched out, if that has any influence at all, and a complete head to head

with the monoclonal antibody.

I think we're going to get enough from the healthy volunteers to see the issue of interference and everything else, that you don't have to do that in the animal models, but I think the animal models really have to focus on that monoclonal antibody, either by itself or in combination as the cocktail with a head to head on the HRIG.

DR. BADEN: I'm going to take chair's prerogative and organize the discussion a little bit, because I think the potential for us to go in many different directions is very high since the data are so rich. What I'd like to do is to structure the discussion in four part, utilizing what has been proposed to us.

The first part of the discussion will be what's needed in vitro, and we should all comment on what we think will strengthen the in vitro portfolio. The next will build on the animal concept. The next will be the human studies in the non-exposed and then the human studies in the exposed cause. I think we'll have a stronger set

of information to the agency if our collective comments and discussion are thematic.

So I agree with Dr. Weina's comment, but we will continue that discussion when we go to the animal part. I think the in vitro part may be relatively straightforward, and I will start by saying in the in vitro part, I think there needs to be a clear understanding of the globally circulating strains, old and new world, that have caused human disease, which includes acquiring more strains if there aren't adequate strain representation from key regions.

I accept the comments from Dr. Ellison that there may be more strains identified than have caused human disease, and we should have a preference to those that cause human disease. We should in the in vitro assays know which are neutralization, easy or hard, and make sure that we have a spectrum -- both genomically, we know the conserve nature of the epitopes of interest, and in vitro understand the resistance profile so that the monoclonals can be selected that have a strong

rationale that they're active against the known circulating strains genomically and the known circulating strains in vitro from a neutralization standpoint.

That would be predicate data that one would then, in the animal experiments, build on. But I think that would be an initial way to comprise what the monoclonal should look like, and whether it's a 2 complement or a 3 complement, there can be a rationale for the complementary antibodies for the epitopes as well as the global strain diversity. Then one can do many in vivo studies to characterize the monoclonals with the known viruses to reassure ourselves that it has the spectrum of interest.

Dr. Ellison, you have a comment I hope to build on and not vitiate my comments.

DR. ELLISON: Those are excellent; I agree. I'd also like to see the EC50 independently of the mAbs, if they are a cocktail for instance I'd like to see if there's variation in the neutralizing capacity based on the strain. I think that would

be useful; also to ensure what epitope they bind to is linear conformational, make sure they're not overlapping. Those are the things I would consider or want to see off the top of my head.

DR. MOORE: I agree with both of those. The only thing I would add is I would like to see that when the in vitro test is done, that the challenge viruses are all equal in strength and that there should be evidence that that was determined before the testing.

DR. BADEN: We don't need to all be in agreement. It is okay for us to disagree. What I think is important is the rationale and thinking is shared so that the agency can hear the different lines of thought to be incorporated into their planning.

Dr. Burgess?

CAPT BURGESS: Just to follow on to the point, I completely agree that because of the importance, particularly for a U.S. indication, that diversity and antigenic diversity of particularly bad variants, not only that the virus

dose that's used in that in vitro assay be standardized, but also that there is reason to believe the flip side of that, that the cell type that the infection is occurring in is not artificially altering the perception of the potency of the antibody.

DR. BADEN: And the presumption of my comment, or an assumption in my comment, which is challengeable, is that one will have one product that's globally deployable rather than regionally deployable because of the practical implications. But that has an implicit assumption, where one could have an enhanced product for a geographically prevalent problem, but I just see the deployment and scalability, and approvability, and social usability too complex to make it viable. But that is a presumed assumption in the way I framed it.

CAPT BURGESS: But just a quick follow-on to that, I think the difficulty in regionalization is increasingly high, is exponentially high, when you get beyond in vitro neutralization or other antibody effector function activity. So the

emphasis should be on assessing potential regional variation, particularly in the in vitro infection neutralization assay.

DR. BADEN: And if I accept Dr Ellison's comments about the 4 cases in the last couple of years in the U.S., there is value in having a product that's active against variants in different species because of the cases that have occurred domestically. Therefore, the premium on making sure it's pan-protective and not a variant specific, because you really don't know.

Dr. Swaminathan?

DR. SWAMINATHAN: The rabies, I'll just address this, but I wonder if in addition to ensuring breadth of reactivity and potency of neutralization, once that has been optimized, whether concern needs to be paid to whether or not the epitopes are in more or less invariant regions of the genome, and whether that's practically feasible to optimize selection of monoclonal antibodies that are less likely to be escaped by mutation.

DR. BADEN: Dr. Ellison?

DR. ELLISON: That's important. I think that they should also demonstrate that if there isn't escape, the other antibody in the cocktail should be capable of neutralizing.

DR. BADEN: Well, are the escape variants well understood?

DR. ELLISON: No. They're artificially made.

DR. BADEN: Yes, so it becomes hard to know what the in vivo selection might be.

DR. ELLISON: No, you would produce the escape, and then you would ensure.

DR. BADEN: In vitro.

DR. ELLISON: In vitro.

DR. BADEN: Yes, but it's hard to know the applicability in vivo because of different selection system so to speak.

Other discussion on the in vitro challenges that should be thought about as part of a package to move forward?

Dr. Ellison?

DR. ELLISON: Who's going to be responsible for conducting the surveillance for this variance? The surveillance center at CDC, we only focus on plus and minus, rabid/not rabid. We typically don't go down to the molecular level unless there's a need to see that, investigate an outbreak, or something like that. And most of the phylogenetic studies that are done are not whole genome. They're based on actually a different gene altogether, nuclear protein, very highly conserved.

The glycoprotein is what we're talking about today, so who is responsible for conducting that type of surveillance?

DR. BADEN: I'm not sure we'll be able to answer that question and establish a new global system for monitoring rabies. However, I think what we can put forward is do we think that's an important piece of data to have? And if we think that's an important piece of data to have, then that can be something that we can suggest would be useful in a product development schema, so to speak. But your point's well taken as to who will

do it, under what aegis, under what quality, is not a straightforward matter. But do you think it would be important to know that, and how important?

DR. ELLISON: I think that would be incredibly important. We discover new lineages all the time. Also, taxonomically, there's only one species that's rabies. We've made these variants and strains ourselves. They're all arbitrary. Phylogenetically and taxonomically, it's just one virus, rabies. It has been compartmentalized into multiple hosts, and they do have independent signatures, but there's no formal naming structure for what we're calling variants, or strains, or isolates.

DR. BADEN: I think they're two different issues. One is to taxonomy. The other is the strain acquisition and sequencing so that data exist.

DR. ELLISON: I think that it's complex.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Mine is just a general comment, kind of agreeing with what has already

been said. I think, especially in this case, where the standard of care, what we have now is already very effective, I think the bar, whether in vitro, or clinical, or preclinical, the bar here should be really high. We need to ensure that whatever monoclonal antibody we have is broadly neutralizing against all the strains that are potentially available there.

So I think it will be important to see strong evidence of efficacy before this moves forward, and we will discuss that more as we move to the human data element with its ceiling challenge.

Dr. Weina, more on the in vitro discussion?

DR. WEINA: Yes, a really great intellectual question about monitoring for the strain variants and everything else, the question that pops into my head is so what? Really, I mean, how is that going to change what we do? We have a vaccine that hasn't changed. We have HRIG that we've been using that hasn't changed. We haven't changed the way that we produce the HRIG, and we haven't modified

it based upon the variance or possible shifts or escapes in it.

So the question is, while that intellectually is a really great question and may potentially come into play down the road, how does that really influence what we're doing in the development right now?

DR. BADEN: I think that's a terrific question. Do you think there's a difference between HRIG, polyclonal, and a monoclonal in terms of its potential activity against different strains, and is that relevant in the development path? Which you're arguing it may not be.

DR. WEINA: I'm arguing that it probably isn't where we're talking about taking at least 2 monoclonals that are in overlapping regions. We still treat diseases that mutate like crazy with single drugs, and then wait until they just don't work anymore, and then come up with a new drug instead of doing what we do with HIV and treat with 4 drugs. That's basically what they're doing with the monoclonal in India, is waiting until they have

something that escapes, and now they have to come up with another single monoclonal. We're just jumping ahead of the game there.

DR. BADEN: Dr. Burgess, did you have a comment on this?

CAPT BURGESS: I might take the opposite view that I think the bar is higher for a monoclonal cocktail that might just target 2 epitopes, and that to me increases the importance of understanding the potential for epitope escape, compared to the standard of care, which is polyclonal and polyfunctional.

DR. WEINA: But that's assuming that the polyclonal, all of the different components of the polyclonal are important in the efficacy that we're observing. What if it's only a single monoclonal attacking a single glycoprotein that's actually doing anything? We don't know the answer to that, so it may only be one that's actually doing anything, and all the other garbage that we have in there is just carrier.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Virologically, that's generally not true, that the serologic response to the capsid or the entire glycoprotein structure of the virus is extremely multifaceted in most cases. So the polyclonal response not only consists of multiple epitopes among one or more dominant proteins, but in fact includes multiple epitopes and multiple glycoproteins, depending on the complexity of the virus.

So I would think that it's highly unlikely that even though all of them may not be important, that they aren't multiple extremely redundant neutralizing capacities in HRIG. I think that's why it is potentially important because this has worked all the time without any problem being made the same way because it's essentially not one monoclonal; it's a whole boatload of monoclonals. It's a multiplicative function as to how likely it is that a given variant strain would escape 2 monoclonals versus the number of reactivities in the polyclonal preparation. So I would be concerned about that issue.

DR. WEINA: No, I understand. But I think the point that I was trying to make is that I kept hearing probably and maybe. And we don't know for sure. When it comes to the immune system, we're like stone-age men looking at the inside of a computer and saying, "Hey, if I poke this, it'll spark." Unfortunately, that's true; that's my opinion.

DR. BADEN: I'm catching up to your imagery.

(Laughter.)

DR. BADEN: Dr. Green?

DR. GREEN: I have a comment and a comment. The first comment is what we do know is the polyclonal is generated by giving the vaccines. So we know that our vaccine, which we think is effective, is generating multiple epitopes and not a single epitope. So this gives you pause about settling for one.

Maybe the solution is you either invest your money in saying we're going to make a cocktail that has more than 2 epitopes, even though the WHO decided 2 was adequate, and they have much more

expertise than I. I don't know the data nor understand the basis for that decision, but whatever the cost is to put 3 or 4 or 5 in, versus the cost to do the collection of virus that's out there to see if the mutant epitopes are prevalent or not, that's an economic question, because you could make a larger cocktail.

It just would cost more money to develop and it would probably cost more money to deliver versus collecting the specimens, which as soon as you're done collecting the specimens, you'd wonder if next week there was a new resistance mutation that emerged.

So I'm not sure of the answer, but in the end, I think that's an economic decision that you're looking at, and that could be decided -- if the economics are prohibitive on both sides, there may not be a sponsor interested in taking this up anyhow and that we don't even have an endpoint to all this conversation.

DR. BADEN: So I think we have clarity on the in vitro requirement. Any other suggestions on

the in vitro? Your point's well taken, and that is part of what will have to be weighed since we don't know. When you don't know, the risk is harm, versus you don't know and you're trying to move something forward. That's one of the challenges the agency is going to have to balance.

So if there aren't other comments on what would be beneficial in the in vitro package, then we'll move to the animal package, which I think Dr. Weina already provided a discussion about features to consider and how to look at the components individually and together. I think Dr. Green has more discussion on that.

DR. GREEN: This is to add to what Dr. Weina said, is what you're looking at. We keep saying human RIG, human RIG, human RIG, but as I understood it, parts of the world that we would be doing our clinical trials might be using equine RIG, which then suggests that when we're doing the in vivo studies, we should include a set of experiments that also look at equine RIG because that's the comparative that's likely going to be in

place.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: If we could just transcend the junction that we just made on the animal side to ask the question again -- and this would be a question of rabies experts -- would you consider an antibody that didn't appear to have neutralizing activity in the available neutralization assay but which had binding activity, and then demonstrated protection in an animal model if a sponsor chose to do that? Which is a different existential question. In other words, would lack of neutralization activity in what's articulated here as step 1, be a dead end?

DR. BADEN: So gatekeeper.

CAPT BURGESS: Because I would say no, but I'm not a rabies expert.

DR. BADEN: Dr. Moore or Dr. Ellison, would you wish to engage?

DR. MOORE: I would say from the publications that I know that have looked at monoclonals that are comparing monoclonals that are

neutralizing compared to monoclonals that are just finding, that you definitely need to have the neutralizing component; otherwise you're not going to stop the virus. I haven't known of any animal studies that have done that just in vitro.

DR. BADEN: So to amplify Dr. Burgess' point just for the record, the question is, is neutralization really the proper gatekeeper since we don't understand protection? And may developers want to think about that as they develop their in vitro package? Where if they have other reasons to believe that a non-neutralizing antibody may work, they can make that argument, and then it would have to make sense based on the available data. But at this point in time, neutralization is the light post, pending information that can be directive.

Dr. Siberry?

DR. SIBERRY: In terms of the animal challenge studies, I just want to confirm that we're recommending that there be both a challenge that's immunoglobulin alone, the monoclonal against poly, and then immunoglobulin with vaccine, because

I think part of this is understanding how it would be given in humans if it got that far and also the potential for interference.

So am I understanding correctly that we think both of those sets should happen with and without vaccine?

DR. BADEN: I don't think it's we. Each of us should be putting forward things that we think are relevant to be considered in the preclinical package. And if I hear you correctly, that the proper studies preclinically in the animal model should include the novel product, and as previously mentioned, may even do it individually, as well as in a cocktail, and with or without the vaccine adjuvant, so that one understands how that behaves.

I would build on that in the sense of -- and I know that the ability to do human studies are here, but one could imagine the Animal Rule not applying to this, but there are parameters associated with the Animal Rule that could fortify the data presentation, where one could imagine to animal challenge models done in a way that could

show efficacy as supportive data to the overall packet that demonstrates.

That I would defer to our experts as to which animal model recapitulates the disease well enough to be able to demonstrate efficacy; and that's, in addition to defining the elements, it's doing the studies that show the final product behaves in a way that would be reassuring. I think that might also strengthen a packet that would provide evidence, given what we can do in well-controlled circumstances, because I think Dr. Follmann's many points about you don't actually know if they were exposed is going to be a fundamental challenge in any human exercise of studying this.

Dr. Brown?

DR. BROWN: I'm sorry. I'm a little bit slow. I wanted to go back to the comment around if we were looking at a mAb that demonstrated binding but not neutralizing, I actually think that that would have consequences for the rest of what has been proposed for how we would -- like the

serologic endpoint conversation and everything. So I actually think that's a bigger issue and might make it a no-go, at least for this proposed pathway.

DR. BADEN: I'm not sure I -- so if we were to consider binding alone, then the rest of the discussion we're having is undermined?

DR. BROWN: Yes, because we're relying so heavily on neutralizing antibody measurements for some of our endpoints.

DR. BADEN: To work with your point, let's say that there was some other assay developed that we haven't thought about today, but three years from now, technology advances, and there's a better way to measure an immunologic parameter that we think is much more tightly correlated with protection. Couldn't that then just replace the discussion for the mAb?

DR. BROWN: Yes, absolutely, but I've been working in rabies a long time, and I'm not a virologist, but this has not changed. This is what we know about how to measure surrogates of

protection. I'm having a hard time imagining something that's going to show up in the next three years. However, theoretically, yes, you are correct.

DR. BADEN: Because to minimize vitiating our whole discussion, I think that if we look at the in vitro element as what are the state-of-the-art data that establishes the in vitro activity? Currently, it's the mAb discussion; our discussion is based on that.

If something were to emerge that takes its place, my hope is the field would use the latest science to guide the discussion, but that would then alter how one assesses the surrogate or correlate, and I would hope that we would be open to the latest innovation based upon what technology can do.

For the purposes of our conversation, we're going to call that the neutralizing antibody because that's the current state of the art, but I accept the point that that state of the art should be fluid with the state of the art at the time the

discussion occurs; so point well taken.

Back to the animal discussion. I think Dr. Burgess, didn't you have a comment?

CAPT BURGESS: It was just a follow-up on two relevant models that recapitulated disease, but the comment I think we heard that that may limit the strains that could be assessed.

DR. HARRIST: Just to follow that up, I do think, if it's at all possible, to think about use in the United States, those bat strains that we know are most common here. I would like to see that if at all possible.

DR. BADEN: Other comments on the animal model element? Dr. Follmann?

DR. FOLLMANN: Yes, a couple comments. There was discussion earlier on the animal model about it would be nice to look at diversity of challenge viruses I guess. If you're going to do that, and there's utility in doing that, you might want to have a placebo group, an HRIG group, as well as a monoclonal antibody group. I don't know if you were thinking just using monoclonal antibody

versus placebo would be efficiency; you'd need 3 arms.

Then just to follow up on a comment Dr. Siberry made, where I think he said you'd want to study this without vaccine, basically, the monoclonal without vaccine. And that could lead to I guess useful information, but if it fails there, how bad is it if it's always going to be given with vaccine?

If we were looking at a vaccine that had peptide and adjuvant, we wouldn't care about how the adjuvant alone or the peptide alone worked. So if it's going to always be given in combination, that's the relevant thing. And if you're going to do that, just monoclonal antibody alone, you'd probably want to do HRIG alone as well to see. Maybe it would fail also.

DR. SWAMINATHAN: So I think you clearly have to do it with vaccine. I thought I had heard a proposal that you also do it without vaccine. And maybe I misheard.

DR. WEINA: No. I think it's important that

you do it without the vaccine. I think it's critically important to tease out how much are we actually getting, protection-wise, without the vaccine being present at all. Without wound cleansing being present, without vaccine being present, how much protection are we actually getting from the equine or human?

I think that was a great point to try both, and this would ideally, I guess, be 4 arms: placebo, 1; equine, 1; human, 1; and the monoclonal, but without the vaccine. I think that that's critically important to do it without the vaccine.

But that really needs to be teased out.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Maybe I misheard before, but I heard it at least in one of the animal models that a vaccine actually doesn't do much, or anything. So I think we have to be cognizant of the limitations of the implications. You have to compare something where HRIG actually works, and that's sort of the crux of it, to me.

DR. BADEN: The issues of the model, and the strain, and the clinical phenotype are all persnickety. So making sure that the intervention gives the result you're interested in, given the limitations and challenges of the model.

DR. SWAMINATHAN: And that was part of the problem with thinking about just actually having one animal model because we know from doing drug trials that even when you have 2 animal models and they show absolutely nothing, you put it into a human and all hell breaks loose. So you're always doing that.

DR. BADEN: Dr. Follmann, did you have a follow on or not?

DR. FOLLMANN: No.

DR. BADEN: Any other follow-on -- Dr. Green? Sorry.

DR. GREEN: I just want to support the notion of doing it with and without. I think it does give you some sense of biologic activity, and if the vaccine didn't work at all, then you wouldn't need to do it, but you wouldn't need to

give the vaccine. This gives you just some sense.

It also may give some -- if you're really going to do this completely, you also, as I think was discussed, are going to do your intervention at delayed times and early imprompt times. So you expose 6 hours, 12 hours, 3 days, 7 days with and without vaccine. And you could almost imagine that the more effective the antibody is, the more important it is if you have delay. Because you're going to always have that built-in delay for the vaccine to go, and when you cross a certain threshold -- and we've heard earlier that once the virus hits the central nervous system, it doesn't matter what you do. So getting that sense of single potency gives me some sense of -- I'd like to know that.

If you had a family that had been bitten and came in belatedly for whatever reason, you would feel better to know that you had some sense that this thing has activity on its own because you're not going to get anything from the vaccine for a couple of weeks anyhow.

DR. BADEN: I think, in part, the animal model is so important because it's a highly controlled known infection, even though the model is extremely difficult. And once we go into people, we have no idea if there was an exposure. We have ways of trying to assess the risk, but ultimately, other than the 20 cases where they bring in the animal's head that can be dissected, it's extremely unusual to have confirmation.

Dr. Follmann?

DR. FOLLMANN: Just a brief comment on Dr. Green's comment, I think a better way to study that, the concern about variable times coming in, would be to give vaccine and antibody variable times after exposure in the animal model. Because generally they'd be getting antibody and vaccine, so you'd like to know how efficacious it is after 1, 2, 3, 4, 5, 8 days delay from exposure in the animal model.

DR. GREEN: I'm not disagreeing with that. I'm saying I want to see both aspects of it, again. I just think of it as someone who treats patients,

to have a sense of what it does on its own gives you some sense of potency, really. So if it turned out that you got some efficacy from polyclonal alone that you weren't getting from the cocktail of monoclonal, I would just give pause, particularly for approval in the United States, which means it might become the alternative approach, that you might be using a product that's a little bit less efficacious, a little bit inferior, you don't know, and you'd be offering it as an alternative to something that's available and efficacious.

I get in a shortage scenario, it would be great to have that backup. But if it was your little child that was asleep and woke up with a bat, and particularly if they tested the bat and it was positive, you would just want the maximum that you could give because if you fail, you know, it's fatal.

DR. BADEN: If no further discussion on aspects of the animal model to consider, then we can open discussion on the phase 1 human data, non-rabies exposed. What kind of well-controlled

human data of safety, efficacy, however we define it in a sort of that phase 1 model?

FEMALE COMM MEMBER: Can you bring up the slide with numbers? [Inaudible - off mic].

DR. BADEN: But is that numbers for the phase 1 or is that numbers post-exposure?

FEMALE COMM MEMBER: [Inaudible - off mic].

DR. BADEN: I thought the numbers had more to do with the sensitivity of detection in the exposed. I'm dividing it between healthy volunteer studies, where you understand the kinetics of the Ig and the vaccine response and any interference, which can be highly controlled; and then what to do in the field where there may or may not be exposures because my dog bit me, or more, your dog bit me, and you won't give me the dog.

Dr. Siberry?

DR. SIBERRY: Just to start off, because we had some discussion about children, to say that I think we should make sure that men and women are represented in these since there could be sex differences; probably not, but important; but that

children and pregnant women would only come in likely in the rabies-exposed studies when we discuss them later.

DR. BADEN: Dr. Green?

DR. GREEN: Just men and women and also looking at the range of adult ages. So you want to look at this at people that are in their 20's, and then people that are in there, whatever, 50's, and their 70's, or whatever you can get in terms of volunteers. But we know that we handle things differently at different ages.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Just that these studies should be done in the U.S. and overseas, where we'd be doing the field trials.

DR. BADEN: I think even though we've been reassured that the vaccine response is so powerful that it will overcome the Ig given, I think we need to understand what interference or have the data to reassure ourselves there is no interference, and how much tolerance we have in the variability of the dose and potency of the monoclonal to make sure

it doesn't then interfere with the vaccine take. I think that's easily done and that needs to be done in light of the different vaccines that it might be paired with, at least major vaccines that it's likely to be paired with.

Dr. Swaminathan?

DR. SWAMINATHAN: I just wanted to second what Dr. Green said about the age. We just know from various vaccines how variable the age-related response can be. Also, with respect to what you said, the interference may be much greater in somebody who is not responding optimally to the vaccine.

DR. BADEN: And whether or not there are any genetic backgrounds that may impact response. It was pointed out that the failure with the HRIG in the Iranian study, there wasn't evidence of a vaccine response. You can't say there wasn't, but there wasn't evidence of one, and perhaps there are other genetic backgrounds, or age, or other factors that may influence; so

at least understanding that the response in a

general sense transcends any given genetic background.

Other thoughts on the -- Dr. Follmann?

DR. FOLLMANN: In Appendix C, there was a discussion about how would we define interference if the antibody was above 0.5, I guess, international units per milliliter at 14 days or so, and they suggested three different ways you could do that. The way that made most sense to me was to just pick a later time point when the antibody would presumably be cleared even if it's substantial at day 14, and then look at that.

DR. BADEN: So I guess the question that you're getting at, is it day 7 peak that matters versus day 14, or 28, or a later time point?

DR. FOLLMANN: I wasn't getting so much of that. I think I just wanted to say we want the vaccine to have durable protection. We want it to be above that 0.5, and to me the simplest way to do that would be to measure are you above 0.5 at day 28, 56, and so on.

DR. BADEN: But do we want durable? I guess

I'm not -- is this about durable protection or is this about blocking that initial exposure? Just thinking about the target profile of this, is it that I'm protected for rabies for the rest of my life or the bite last week isn't going to do me in?

DR. FOLLMANN: Well, I think they felt that the correlate of protection is 0.5 international units, so you want to continue to have an antibody above that for a long period of time. So whether it blunts it by a log or two or three, maybe that's bad, but as long as it continues to bump 0.5 for a long period of time, you should still be okay.

Anyway, I was answering a more narrow question, which was what do you do about measuring interference if there's a lot of monoclonal antibody at day 14, three different ways to try and address that issue? And they made three suggestions. I prefer the one that says look at day 28 or 56 to be above 0.5.

DR. WEINA: And toward that point, one of the things that I thought of as I was reading through the Appendix C was the fact that however

long you decide to follow it, you're going to have a lot of lost to follow-up potentially in this population.

So the trial would have to purposefully be looked at so that you didn't have the same requirement of numbers that have their neutralizing antibody measured a year out as they did 14 days out, just so that you didn't lose too many people at follow-up because I've seen that in clinical trials, where they have these extremely long follow-ups, and then we're missing the main point because we're trying to do everything.

DR. BELL: I guess you'd have that luxury in the healthy volunteer versus the exposed patients.

DR. WEINA: But even in healthy volunteers, you might lose some.

DR. BADEN: But in the healthy volunteers, should this be placebo controlled? Should this be active-comparator controlled? These are not exposed individuals. What's the right way to make the assessments that we want them to make?

DR. GREEN: Two comments. First to what you

just asked, I think because you're looking at interference, then you do want controls that get vaccine without exposure to the antibody and get vaccine with exposure to the antibody, and then you're going to need various potential vaccines. And you probably have to do the various potential antibodies, so that's HRIG, ERIG, and the cocktail.

Then just to the timing of levels, if money's no object and subjects will agree to -- or participants, excuse me, that's the correct term here -- and participants would agree to it, it seems to me you would want early and a little bit later because you're interested in the kinetics of getting vaccine-associated protection. So if you blunt it totally or just delay it, you'd want to know both of those pieces of information relative to what we do now.

So again, the limitations of this is how much money you're willing to spend and how willing your participants are to come in and be seen and be stuck on separate occasions. But in an ideal world, when you're drawing it up, I would do all

those variations and early and later blood draw.

DR. BADEN: But part of this is what's the critical path of information that would reassure us that the product being developed makes sense? There will always be 101 more permutations, and I think that's part of how --

DR. GREEN: But again, if we think that the real protection is coming from vaccine and that the purpose of the antibody is to cover you until the vaccine gets in, it seems it would be important to know whether or not -- maybe we already do know this. It would be important to know whether or not the new cocktail does anything in terms of timing to getting to the critical point, and to your point earlier, perhaps more importantly is whether you have protection still at a month, and certainly at 6 months or a year. I think that's a different question and a different purpose of the vaccine.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: I don't know if this is critical path or the 102nd, 115th permutation, but definitely route of administration of vaccine,

given ex-U.S. versus U.S. But then the question of not only different vaccines, but as was raised in the background and the extant question about different vaccines given in the same post-exposure series, whether or not it is important to have phase 1 data about vaccine interference in that context. I don't know. That question was asked, but I don't know.

DR. BADEN: We shall move to the exposed, the phase 2B -- I'm sorry. Dr. Troy?

DR. TROY: That applies to the third question. So do we want to wait for that until after the voting.

DR. BADEN: Thank you. I appreciate guidance.

So we have about 10 minutes until a break, so we can do the vote on the preclinical early clinical package, so this is question 2, voting. I'll read the question, and then we can vote yes or no or abstain.

Would clinical trials of an investigational mAb cocktail product as part of post-exposure

prophylaxis in rabies virus-exposed subjects be acceptable if the data package available to support trial initiation included the following elements: cell culture data demonstrating breadth of coverage -- we've had that discussion -- animal challenge studies demonstrating survival benefit; and clinical studies in healthy volunteers, not rabies virus exposed, demonstrating a similar half-life, comparable early RVNA levels, and comparable vaccine interference of the mAb cocktail versus human rabies immune globulin? If no, what additional data elements would be needed?

So we'll pose the question. If these data, as we've been discussing, were available, would this be a foundation that would allow a trial to go forward in exposed individuals? After we vote, then we can highlight any elements that have not already been highlighted.

The voting has been initiated and your light should be blinking. It will keep blinking, and you can press it as many times until the blinking stops, and that's where your votes stands.

(Voting.)

DR. BADEN: The voting results are 16, yes; zero, no; zero, abstaining; zero, no voting.

So what I would open now -- and when we can start on the right side of the room with Dr. Brown. You don't need to reiterate what we've already said. If there's anything that we haven't discussed -- and this would have been more important if someone had voted no as to what would be missing. But if there's anything that has not been discussed that should be highlighted, we'll go around the room and everyone can highlight that, and then we'll have the break before we go to part 2, which is the more challenging element.

Dr. Brown?

DR. BROWN: I don't have anything to add.

DR. BADEN: Dr. Moore?

DR. MOORE: I don't have anything either.

DR. BADEN: Dr. Ellison?

DR. ELLISON: Nothing to add.

DR. BADEN: Dr. Harrist?

DR. HARRIST: Nothing.

DR. BADEN: Dr. Baker?

DR. BAKER: No additions.

DR. BADEN: Dr. Porter?

DR. PORTER: Nothing to add.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: Nothing to add.

DR. BADEN: Procedurally, we don't need to confirm our vote. Okay. I need to stay on the right side of the rules.

Dr. Burgess?

CAPT BURGESS: Nothing to add. I voted yes.

DR. BADEN: Okay. We'll have to start again with Dr. Brown.

(Laughter.)

DR. BADEN: Just say what your vote was.

DR. BROWN: I voted yes.

DR. BADEN: Dr. Moore?

DR. MOORE: I voted yes.

DR. BADEN: Dr. Ellison?

DR. ELLISON: Yes.

DR. BADEN: Dr. Harrist?

DR. HARRIST: I voted yes.

DR. BADEN: Dr. Baker?

DR. BAKER: Yes vote.

DR. BADEN: Dr. Porter?

DR. PORTER: Yes.

DR. BADEN: Dr. Burgess, I'll skip. You already voted yes.

DR. BADEN: Dr. Ofotokun, what your vote was and if anything to add.

DR. OFOTOKUN: I voted yes, and I have no additional comment.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Yes, nothing to add.

DR. BADEN: Dr. Clark?

DR. CLARK: Yes, nothing to add.

DR. BADEN: Yes, nothing to add.

Dr. Weina?

DR. WEINA: Ditto. Yes, nothing to add. Sorry.

DR. BADEN: Please vote yes so I don't have to re-vote.

Dr. Green?

DR. GREEN: Yes, nothing to add.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Yes, nothing to add.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: Yes, nothing to add.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Yes, nothing to add.

DR. BADEN: So it is now 2:54. We will take our break.

Can we resume at 3:10? And we will take up the second half of the discussion. We're now on break.

(Whereupon, at 2:54 p.m., a recess was taken.)

DR. BADEN: Time to take your seats. We shall resume the second part of the discussion and voting elements. I would like to thank Dr. Troy again for keeping me on target.

(Laughter.)

DR. BADEN: The way we will proceed is element number 3 in our handout, or question number 2, or discussion item number 2, which is associated with question number 2. We will discuss

the issues that we think are relevant for a biologic license application, a BLA, and that will get into the elements of what types of studies in exposed individuals and what kind of safety are needed. We will then vote on whether or not we think the path proposed is a reasonable one for potential licensure consideration.

After we have that vote, you can put up the question or the discussion element. After that, we will then have any postmarketing discussion. So the discussion and question will be around the elements appropriate for a BLA application; afterwards, what additional information will be valuable in a postmarketing setting. So we'll try to separate those two elements.

Discussion item 3, which is really discussion item 2 for question number 2, this discussion item is information needed to support submission of a biologic license application, BLA. In addition to what we've already discussed, cell culture, animal challenge, healthy volunteer clinical data, please discuss the type and amount

of clinical data in rabies-exposed individuals needed to support submission of a U.S. BLA for a rabies mAb cocktail as part of post-exposure prophylaxis or PEP.

I'd like to open the floor to discussion of the elements that would be valuable for to support a BLA for approval. Dr. Green?

DR. GREEN: Dr. Baden, I was wondering if you want to direct this as you did with question 1, since there's an A, B, and C to this approach as well.

DR. BADEN: I wasn't planning to --

(Laughter.)

DR. BADEN: -- in that I think that this element will require a discussion of all of these factors, and I'm happy for you to discuss A, to start discussion on A, but I think they're going to be heavily intermixed because I think the issue of a thousand participants with the mAb and the lack of mortality in 750 may have some overlap as to who those individuals are.

But we'll open the floor to discussion, and

I think that some of the power discussion, some of the assumptions of a 99.5 percent versus a 99.9 percent, the tables that you had previously referenced, Dr. Green, related to what level of power do we think is acceptable to be able to move forward, realizing there will always the potential for more data to have greater precision, and what level of precision is adequate to move forward given the potential utility of having more products in this space.

Any takers to start the discussion? Dr. Kartsonis?

DR. KARTSONIS: I just would make one comment as it pertained to the lack of mortality in greater than 750 subjects, which I think makes a lot of --

DR. BADEN: Speak closer to the microphone, please.

DR. KARTSONIS: Oh, sorry. I just wanted to make a comment about the lack of mortality in greater than 750 subjects. I would ask that we also consider, if we are going to also have an

active control group in there, whether or not -- that it would be also -- my worry is you may end up having 1 in 2, or 2 in 2, depending on the type of cases you get. My worry is about a very strong lack of no mortality in 750 may need to be balanced relative to what you also see in the comparator group. That was the only thought I had in terms of that.

DR. BADEN: Point well taken, but to expound on the principal, I think the principal is if there's a comparator, then one can have some assessment if the misbehavior is disproportionate, although it's very hard in this setting to assess that because the anticipation is 0 and 0 or it may be 1 and 0, and just random between the two groups, depending on the environment, the exposure.

But how do we feel about the 99.5, putting forward that 99.5 is adequate to move forward in this ceiling effect situation and opacity as to the nature of the exposure? So we're not really clear on the ceiling effect. Dr. Harrist?

DR. HARRIST: Thank you. Well, I think it's

been said before, too, but I would agree that as somebody who would be recommending post-exposure prophylaxis to somebody, and knowing that we had something that's 99.9 percent effective, again, that's sort of a guesstimate, too, but it's the best information we have, versus something that's 99.5 percent, and that hasn't likely been studied in the United States very extensively, it would be hard for me to either recommend equally or to recommend the monoclonal antibodies with the 99.5 percent.

Now, in a situation where there wasn't HRIG available, then, yes, I think it'd be great to have, but it's hard to picture a scenario in which I could --

DR. BADEN: So are you arguing or -- I don't mean to be argumentative, but are you sharing a perspective in the sense that adequacy for approval or adequacy to recommend?

DR. HARRIST: Adequacy to recommend.

DR. BADEN: But could you imagine approval at let's say 99.5, realizing that practitioners

would have to be aware of that, and that might influence selection of agent, at least locally?

DR. HARRIST: Yes, I think that's fair.

DR. BADEN: Dr. Weina?

DR. WEINA: I just wanted to comment that the idea of lack of mortality in greater than 750 subjects is -- in an ideal world, yes, it would be really great to have that. But trying to look at it from a practical standpoint, the Indian trial, 2 years to do 200 people, given the issues of recommendation, we've got something that's 99.9 percent effective already, are you going to take a chance that you're that one bad guy in the group that's 99.5 percent? Are you really going to enroll in that trial or not?

Then there was variability -- the point I want to get to is that we have to be practical in the standpoint that you can't restrict the enrollment to only people that are going to get there within 24 hours and get everything ideally placed and everything else. But if you're going to say, hey, we need 750 people to reach this area,

reach this limit, we have to be really careful that everybody is assessed at the time that they get it for the adequacy of how it was administered, when they came in, and everything else, and try and enroll as many as you can, but get as much data as you can on every single one, so that you can do an adequate post-mortem if you have to or if they don't make it, and see if it's reasonable that they died; otherwise you're just never going to get the numbers. You aren't going to get a sponsor that's going to do a 20-year study to enroll 750 people.

DR. BADEN: So are you suggesting that there should be a phase-in of the nature of the exposure, where the non legs first, there's some evidence that it doesn't fail, and then you move to a higher risk, or do you think you should just go right to higher risk?

DR. WEINA: No. I think the initial one that they're talking about, that they had suggested in which you take lower risk individuals first and then go to the higher risk individuals is fine. But I still think that you have to try and make

sure that in our search for as much perfection as we can, so that there's not a lot of Monday morning quarterbacking when everybody really wants the vaccine, but they don't want any risk associated with it, it's just not realistic.

So at some point, you have to balance the practicality with the idealism that you're going to get a perfect vaccine, which you're never going to get.

DR. BADEN: Dr. Swaminathan, did you have a follow --

DR. SWAMINATHAN: The concern I have about recommending something that one can't say for certain is noninferior is real, but as I think you pointed out, it needs to be divorced from whether we're talking about valid -- rationalizing a license application or making a clinical decision on the use of that agent.

There are many drugs that are in guidelines as second-line use when the first drug can't be used, isn't available, or in a mass casualty setting, for example. And without the existence of

those alternative agents in some of those extenuating circumstances, it would be extremely difficult and could lead to mass morbidity and mortality.

So I think there are public health reasons to support an application that may not completely overlap with individual clinical decisions.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: When I came here, I was thinking of this more as 750 gives you -- if you have zero mortality, you can have 99.5 percent survival rate or better, and then we'd go on to the 6,000-person study. This is the way I was thinking of the FDA's proposal, and then presumably we'd rule out 99.9, and just thinking one would follow after the other, not thinking through the issue that if it's licensed, it would be available after the 750 and could be used widely.

But then, in reading the question, I noticed that there were two possibilities. One would be after the 750, it would be available to everyone, or after the 750, it would be recommended as the

second-line therapy. I'd much prefer that sort of licensure or approach because I really want the 6,000, and I fear if -- if it's recommended a second line, there's a much greater chance of getting the 6,000.

So I'm thinking of how would I want to approach this as being available, I'd want the 6,000 ultimately. So I think second line after the 750 would be the preferred a labeling.

DR. BADEN: I guess I want the 250,000 after KEDRAB, but it's how do you get there. It's how do you have the initial data that says it's reasonable to keep going forward --

DR. FOLLMANN: Right.

DR. BADEN: -- and that initial data will be collected in a high-resolution settings, so you have greater certainty in the measurements, because as you get bigger and bigger, you may not be able to measure a car accident. It just becomes harder as you get larger numbers to have the same high-resolution follow-up.

So to some degree, as you are suggesting,

for the BLA, what in the postmarketing, and then what in the post-postmarketing as one looks at different formats of scale-up in different environments. I'm still struck by 17 million treated, 60,000 deaths annually, that there is a current global unmet need that the current available products aren't meeting for whatever reason. I'm not passing judgment as to why we have 59,000 deaths globally, but that is going on, and how to have more tools to help address that, and then would need to collect all the data you're suggesting.

DR. FOLLMANN: Right. So the scenario I don't like is it's approved after 750, you don't get the 6,000, and we don't know. I want to avoid that.

DR. BADEN: Fair enough. Dr. Ofotokun?

DR. OFOTOKUN: I don't even know how we get 750 participants to do this type of study, for two reasons. The outcome we're looking at here, it's fatal. If your product, if it doesn't -- it's not as good as the standard of care. The risk involved

is very high. And the standard of care, as we've seen already, if we do everything right, it's over 99 percent.

I find that if you take this to the field, how do you even tell participants I have a product that is 99 percent effective? I have another product. I'm not sure; it could be quite as effective. How do you even sell that? I wouldn't in good conscience as a clinician, in a clinical trial, offer that to my participant. So I still see a lot of -- I struggle with how do we even get to 750.

DR. BADEN: And you struggle because of how do you portray it to the volunteers --

DR. OFOTOKUN: Absolutely.

DR. BADEN: -- to choose A versus B --

DR. OFOTOKUN: Yes.

DR. BADEN: -- given what's known about A and what's unknown about B.

DR. OFOTOKUN: Absolutely.

DR. BADEN: Despite the small risk but a very serious one. Although in the India study,

they were able to do it, meaning it was doable, and then it's a small number.

Dr. Burgess?

CAPT BURGESS: Dr. Harrist's comment made me think about this. As a practitioner making a recommendation, I like 99.9 percent a lot more than I like 99.5 percent for sure, but this is for a U.S. BLA. I think our confidence in 99.9 percent is about canine rabies. I think our confidence about the effectiveness for other is just less because there's less experience. So I'm struggling with how to weigh that.

DR. BADEN: And I was struggling with the same issue, and I don't know if Dr. Moore or Ellison would want to comment. The 99.9 percent number for HRIG, how confident are we in that number for the kinds of rabies that we see in the U.S.? Because the whole discussion is predicated that that number is a fact, and does it have variability or other considerations that make it less certain?

DR. ELLISON: We have about 30,000 exposures

a year in the United States, 34,000-ish. There's no denominator. We haven't had a failure associated with HRIG in the United States, associated with all the different exposures that happen in all the states. That's the only thing I can tell you.

CAPT BURGESS: Not to take issue with that at all, but there are exposures and there are exposures, and there are recommendations to get post-exposure prophylaxis here that are different than recommendations to get post-exposure prophylaxis in other places.

DR. ELLISON: Absolutely, I completely agree.

DR. MOORE: From what I understand, that 99.9 came from the Philippines, the large --

DR. BADEN: Dr. Troy, please?

DR. TROY: Actually, the Philippines would be 99.99 percent. The 99.9 was from the field trials, that there's lots of variability.

DR. MOORE: I consider the variability, especially in developing countries where deaths may

not be recorded to rabies, so I kind of take that into consideration, too. It is a number, but does it include everything?

DR. BADEN: Dr. Swaminathan? No? Okay.

Dr. Green?

DR. GREEN: Yes. I wasn't certain how many of the subjects or participants that are not getting the composite monoclonal need to get ERIG versus HRIG. The bullet that we're going to be voting on actually only mentions HRIG, so I wanted to clarify, as I've clarified earlier and as we've, that we need to have that be ERIG as well. But I don't know whether now you have to think about is a thousand adequate because then you only have 125 of each of those, or is it if you're in the United States and we're only doing 100 people or 50 people in the United States, they get HRIG, and if you're outside, you get it there, and how that impacts on comparability.

The data that you just quoted to us from the Philippines, is that with ERIG?

DR. BELL: In the Philippines, 96 percent

get ERIG free [indiscernible].

DR. GREEN: So when we go to vote, again, the question as posed we're voting on says HRIG, and it's going to be a caveat that it's not going to all be HRIG, and maybe very little bit is going to be HRIG, but we just have to take that into consideration and make that as a statement with the vote that we give.

DR. BELL: Can I talk? I'm sorry.

DR. BADEN: Yes, Dr. Bell?

DR. BELL: The discussion that we had internally was if it's for the U.S. s population, HRIG may be an appropriate comparator, but some people's opinions might be that ERIG should be done.

DR. GREEN: But does that imply, then, that if you're doing the study in Africa or India, that you're going to ask the sponsor to use HRIG because it's to get a U.S. indication?

DR. BELL: That's a good question. It significantly adds to the cost of the development.

DR. BADEN: Is it to the U.S. standard or is

it to what is the clinical standard, if you're trying to understand how the new therapy behaves? Because ultimately we want to understand how the new therapy behaves, which I would think would be related to the clinical standard rather than the local standard, local meaning just the U.S.

DR. BELL: We had discussion with ethicists at the public workshop, and some discussion was in areas where they have different access to therapy for that indication, for example, PrEP, it might be ethical to do what's the standard of that location. But if we were to approve this product for the U.S. population where they get HRIG, that's where some people were grappling with should the comparator be HRIG or HRIG versus ERIG.

DR. BADEN: Well, hopefully the breakthroughs will be close to zero, so it may turn out to be similar.

DR. BELL: I mentioned capturing the rabies, I looked back at the transcript from the public workshop, and the doctor from the Philippines said that in 2006, they got 200 animal heads, and 30

percent were diagnosed as being rabid. In the center, they have 3,500 exposures in 2016, so that's the ballpark of definitive rabies from the animal.

DR. BADEN: We have several follow-ons. We'll do Dr. Weina.

DR. WEINA: Again, whether we use HRIG or ERIG as the comparator would depend upon the entire package. So if the animal data showed that HRIG and ERIG were equivalent with the monoclonal, then would it really even matter in the clinical trial whether you use HRIG or ERIG, right?

DR. TROY: I think one issue, since HRIG is the only product approved in the United States in terms of the safety comparison, HRIG would be more relevant, I think, for approval in the U.S., even if ERIG is used more often globally.

DR. WEINA: And just makes getting 750 even that much harder for a sponsor.

DR. MOORE: If I remember from the 2017 workshop, representatives from Taiwan, Thailand, and the Philippines made it pretty clear that in

their minds and their experience, ERIG and HRIG were equally effective, so there's that. Then also, if this study is done in other countries, are you going to accept the post-exposure prophylaxis vaccine schedule as far as route and days?

DR. MURRAY: I think with the ethics of research, though, we have to do somewhat of a clinical standard for the locale. We can't substitute something that that community won't get in the future, and then take it away. So for the data to also be applicable to them, we have to use I think the local standards. I think there's a principle related to that, an ethical principle, the way you would do research.

I think ERIG and HRIG are pretty similar. They appeared to be pretty similar when we looked at the clinical trials as far as failures. I think the difference might be more so in the safety and some of the adverse reactions. So I think there could be a recommendation for maybe using HRIG, where it's acceptable in that community, but I think clinical trials would have to be kind of

flexible to a clinical standard, and that's my opinion.

DR. BADEN: And you will have the failures in the novel treatment, which ultimately is going to drive the assessment. The absence of failures in the novel treatment makes it easy to compare to whatever you are comparing it to, and an overwhelming number of failures would be problematic.

DR. MURRAY: And I think the nuance, the difference between using ERIG or HRIG as a comparator kind of pales to the overall uncertainty we'll have with the amount of data.

DR. BADEN: I think Dr. Ellison had a follow on, and he's been patient.

DR. ELLISON: It was actually a question about the clarity. Will these animals be laboratory confirmed as being rabid?

DR. BADEN: Do you think that is feasible?

DR. ELLISON: It depends on where you're doing.

DR. BADEN: It sounds like in the

Philippines, they had less than 10 percent of the animals, and only a third of them were confirmed. And I assume where they brought the animals in, there may have been greater concern. I don't know.

I think it would be very advantageous to have it confirmed, have the animal, and really understand the exposure, and measure it from the distance from the CNS. I'm just not sure that that will be practical. But your point's very well taken, and I think that's the issue, is how much exposure is the exposure, and if there's even an exposure.

Dr. Kartsonis?

DR. KARTSONIS: I was just going to make one point about the ERIG versus HRIG. Actually, if the pharmaceutical company is going to go forward with this kind of study and would be providing the HRIG, that may actually be an opportunity to assist with recruitment in the sense that if ERIG is the standard of care or if these therapies are being paid for by the patient in these parts of the world, this may indeed be something that would help

with recruitment in terms of giving HRIG, and to say we normally use ERIG, but HRIG could actually be a safer option for you in that particular region. So it's a way to kind of get recruitment to help you.

DR. BADEN: Sure. That makes sense. I just am always leery if HRIG is not approved in that country.

DR. KARTSONIS: I don't mean --

DR. BADEN: One has to have certain -- and I don't know all the local nuance. But your point's well taken. If the sponsor of the study is bringing both sets of products free of cost --

DR. KARTSONIS: Absolutely.

DR. BADEN: -- as long as there's local acceptance of the comparator.

DR. KARTSONIS: Which obviously the ethics committee would have to approve and the local countries would have to approve as well.

DR. BADEN: And one would hope flexibility on the country, but also flexibility on the agency to be practical as long as the scientific data are

available to give confidence that what was assessed shows evidence of meaningful activity.

DR. KARTSONIS: That's right.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: [Inaudible - off mic].

DR. BADEN: Dr. Ofotokun? No? Dr. Siberry?

DR. SIBERRY: So on this ERIG/HRIG, I think the mortality comparison, they can be combined. I really don't see the value in trying to stipulate it be all one or have separate subgroups. Mortality comparison, they should be combined.

I think it would be feasible to require that the sponsor have enough recruited to do the short-term safety outcomes and serologic analyses and vaccine interference for the HRIG comparator. That's going to be a subgroup. That's going to be feasible. So I think a hybrid approach where you require an HRIG comparator for some of those, that's a relatively smaller number to get at. But then for the efficacy, the mortality comparison, absolutely, either one, they should just be combined.

DR. BADEN: Dr. Porter?

DR. PORTER: I'm not sure that this is an issue that we're addressing, but I can see that there would be a difficulty in enrolling people for the trial, because rabies is 100 percent fatal. So the difference of 0.4 percent is real to patients. I had a low-risk cat bite and went through the whole series because there was this much chance. Though I was familiar with the colony the cat came from and everything else, I still went through with it.

I think even given the opportunity to have the monoclonal antibody, I would've chosen still the HRIG. This is reality because I think if it wasn't a fatal disease, 100 percent fatal, then there might be some play there, but there isn't.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: I just wanted to make sure I understood, how many patients got vaccine and PEP in the Philippines, did you say?

DR. TROY: I can tell you I think it's like 3500 a year, who are WHO category 3 exposures and

got PEP including RIG. There were additional ones who were not WHO category 3, WHO category 2 that just got the vaccine, and then I believe there were some who didn't get the RIG.

DR. SWAMINATHAN: But it was like 3500.

DR. TROY: Yes.

DR. SWAMINATHAN: And the presumed prevalence there of actual rabid exposure is about 10 percent?

DR. TROY: So, yes. It's a rabies-endemic country, but it's on the lower side, so I think it was around 10 or 15 percent, yes.

DR. SWAMINATHAN: But like the heads, it was like 10 percent, right?

DR. TROY: Yes.

DR. BELL: I think it was 200 heads and 30 were -- 15 percent.

DR. SWAMINATHAN: But 10-15 percent or whatever.

So there's really only about 1200 or something a year that had real exposure, likely to have had actual rabies exposure. So this number of 99.99

percent, what's the standard error of that?

DR. TROY: That's of the WHO exposures. That's not of people who were actually --

DR. FOLLMANN: I understand, but thinking about actual risk to people -- antibiotics work really well when you have a virus, so I like to think about situations where it actually might make a difference. So if in fact about a thousand people, it was successfully used and there were no deaths, does that really mean it's 99? Is it 99.5 plus or minus?

DR. TROY: That's the crux of the question. You're right, because we don't have any good data on people where it's confirmed to be rabid and what the percentages are in those cases. We only have data where it's WHO category 3 exposure.

DR. SWAMINATHAN: Then the other question, I was under the impression that equine antibody had a significant risk profile, sort of adverse effects.

DR. TROY: It's improved recently. It used to have a very bad safety profile, and since they've done better purification techniques with

just the Fab fragments and things like that, and now that the rates are much lower. So I think there's still -- and you can correct me. I think they're still higher than with HRIG in general, but it's quite low. It's like 1 percent now for ERIG.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: I just wanted to summarize what I was thinking about the study that would be needed that would be voted on. I think it would be 750 per arm, a randomized double-blind controlled study maybe with HRIG or ERIG, but that would be known by locality. So you could stratify the safety analysis by that, as Dr. Siberry was saying, but mortality would be looked at overall.

We had talked earlier about the issue of exposure and other factors that might impact the risk of mortality and feel that it could be challenging to get that, but I do think we should try to collect that as best we can, including time from exposure if you can genotype the virus that infected or exposed to the human; location of the bite, species, and those sorts of things. I think

that should be part of both the 750 trial and the 6,000-person trial.

Also, the WHO category seems great for decision-making or some kind of risk, but I don't know if it really relates to whether you've been exposed to the virus, and maybe there'd be another way to collect data or have a different or better risk category then WHO has, some that would take into account it wasn't just a dog bite, but you could sacrifice the dog and see that it was, or something like that. So there could be an opportunity to better risk stratify than just the WHO categories.

The other thing is just a comment. There's been discussion about it might be hard to recruit for monoclonal antibody because it's new, but it's been approved in India, so it's possible there would be a lot of experience with the Indian monoclonal, especially if it's competitively priced or disseminated by the government or something. So that could remove the challenge in recruiting for the studies we're talking about.

DR. BADEN: And that's part of how KEDRAB was approved, based upon leveraging other data, and that's polyclonal. So your point's well taken. I just want to push you a little bit on the 750 number. What do you think of the 750 number as the efficacy marker and the thousand number as the safety marker?

DR. FOLLMANN: I was glad the FDA proposed a number and then sort of a concede [indiscernible] to choose that or not. It's like we use p 0.05, and I'm glad I don't have to rethink that every meeting. But the 750 is tied to the 99.5, so that seems like a reasonable green light on the path to a larger study. That's sort of the end of my thinking about it, but it's predicated on the idea we do the 750 study, and then we get the 6,000 study, and then maybe that would be more widely used, and then we could get more data. So a graduated approach to information.

That's my view on the numbers for mortality. The thousand on safety, I guess that's a common number the FDA uses for safety, and I have no

dissension from that.

DR. BADEN: And the 750 on the way to approval and then the 6,000 in the postmarketing category doesn't seem unreasonable to you in a graduated approach?

DR. FOLLMANN: No, that seems reasonable. Importantly, it's 750, the approval for this is a second-line therapy.

DR. GREEN: Dr. Follmann, can you just restate that algorithm that you did. I just want to make sure I understood because you spoke quick, but I always like to pay attention.

DR. FOLLMANN: I was thinking with 750, if there's no mortality, we can know that survival is 99.5 or better. That seems like a reasonable signal to turn on the green light to a postmarketing study and a licensure that says the monoclonal would be used as a second-line therapy, so that would incentivize or make it more likely that we would get the postmarketing study, and then we'd have presumably that information. And if no one died in the 6,000 in the monoclonal, then we

would say survival is 99.99 or better, which is I think good evidence for wide use of it.

So it's sort of predicated on winning on mortality each time, but that's --

DR. GREEN: And the comparator, was that 750 as the comparator?

DR. FOLLMANN: Yes. I was thinking, as FDA suggested, 750 in the initial study, premarketing study, as a kind of reference but not a formal comparator because we expect very, very low mortality. It's sort of a canary in the coal mine or some kind of control for that. And then in the postmarketing study, they were suggesting a 2 or 3 to 1 randomization. So 6,000 on the monoclonal antibody and 2000, say, on the comparator, which also seemed reasonable to me.

DR. BADEN: And this study of course needs to be done where high-risk exposures are present.

DR. FOLLMANN: Yes. It's all sort of predicated on that. I worry a bit about if the U.S. -- like in Virginia if you get bit by a dog and you're going to be a high category, that has to

be thought of carefully.

One other comment. In some of the information, it was saying we could use the 750 as part of the 6,000, and I don't think you should. I think you should do 750 and then do a fresh 6,000 because I don't want to double-count. It just seems better to have a complete independent set of data to get a clear signal.

DR. GREEN: That's a modification of bullet B. That's just the reason why I was getting a clarification. Bullet B is written as 750 participants get the polyclonal -- or bullet B/C -- and at least a thousand subjects get -- versus HRIG and at least -- actually I'm confused as to what FDA was saying now.

Were they proposing 750 versus a 250 comparator or 750 versus a thousand?

DR. TROY: Sorry. So at least 750 who receive the mAb cocktail, who were rabies exposed in rabies-endemic countries, but then at least a thousand who receive the mAb cocktail overall, including phase 1 subjects who were healthy

subjects who weren't exposed, because a thousand would be for the safety; the 750 would be --

DR. GREEN: So you didn't mention in your A, B, and C what would be the comparator size.

DR. TROY: We didn't mention.

DR. GREEN: Thank you.

DR. BADEN: But the 750 in the C could contribute to B. And if there were those who were exposed but deemed to be category 1 or 2, they might go into safety but not count as much towards efficacy. So you don't have to have 2,000. It could be a more modest number since 200 was difficult.

Dr. Weina?

DR. WEINA: Thanks. I'm kind of struggling a little bit and hope to get people's thoughts on the idea of approving it as a first-line indication versus a second-line indication, especially in light of a lot of these numbers, we're just kind of fooling ourselves, really. I mean, because, honestly, surveillance in the United States for rabid animals have consistently bounced around only

5[000] 6,000 animals when they're actively surveilling animals in the entire country for the entire year, and usually between 1 in 4 or 1 in 5 max, human cases in the U.S. every year. And yet we give -- just at Fort Belvoir gives tons of post-exposure prophylaxis for rabies all the time.

So if we're going to be saying it's a second-line indication, do we ever expect in any of our lifetimes to ever actually get 6,000 rabies-exposed people in postmarketing surveillance? The thing is, postmarketing surveillance --

DR. BADEN: I guess my comment would be 250,000 received a non-approved agent elsewhere in the world.

DR. WEINA: Elsewhere in the world, but for approving it in the United States, that doesn't mean it's going to be approved elsewhere.

DR. BADEN: No.

DR. WEINA: And we're not going to do clinical trials elsewhere after it's been approved.

DR. BADEN: No, but that was approved in the

U.S. based upon data from elsewhere --

DR. WEINA: Right.

DR. BADEN: -- and I think that if the question is what's an amount of data to allow approval, I think your point is fair, is that is it first or second line? And then the question is how do additional data get generated and where, but that's more in the postmarketing.

DR. WEINA: No, I understand. But it kind of ties together because if we're going to sit there and say, well, yes, 750 is fine for second-line indication in the United States. But we're talking about approval in the United States, so the postmarketing surveillance, at least the assumption we have to go by right now is that it's going to be 6,000 from the U.S. unless other people approve it as well.

DR. TROY: Sorry. It wouldn't be 6,000 in the U.S. It actually would be 1 to 6,000 in rabies-endemic countries. So it'd be a postmarketing requirement, but it would not be done predominantly in the U.S.

DR. BADEN: The requirement would be where they're highly exposed, but that would require those environments supporting its use in those environments.

DR. WEINA: Right.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: We're having postmarketing discussions; that's the next point, so I hope we'll come back to that as a separate topic. Two quick things. We're talking about FDA potentially having a second-line indication, and I just wanted to confirm that that was what would be in a label as opposed to what a guidelines group would do. That sounds like guidelines terminology to me.

DR. GREEN: It could be in a label.

DR. SIBERRY: Could it be labeled that way?

DR. MURRAY: Well, it could be. Anything could be done in a label. I just don't know what second line necessarily means in this case. It could be based on the type of exposure, the type of bite, single bite. It could be a category 3 that you thought was otherwise kind of low risk. Is

that what you mean by second line, only if HRIG isn't available? That's one other kind of second line. That's a whole another discussion, what is your definition of second line?

DR. BADEN: That's really helpful.

DR. SIBERRY: Again, I feel like often guidelines groups will be thinking about what the clinician in the field and the health departments are doing and help put that in perspective of here are the places that you would use this compared to the other. I don't know that that's necessarily has to be in the label.

The other quick comment I have is I thought the thoughtful point by Dr. Porter about who's really going to accept this, we work with a group who are trying to study a way to get away from HBIG as part of hepatitis B perinatal transmission because access cost was really difficult in this lower income country.

So the group worked with the Ministry of Health in that country, who was struggling also with how do they increase access to an alternative

that might hopefully be as good but would be either cheaper or more feasible. So I think the sponsor should be encouraged to work with ministries of lower and middle income countries where rabies is not only a big problem, but where access to the equine or the human immunoglobulin is a major problem because that I think is where you get the equipoise and then the ability to kind of go into an area with the ministries' support to offer something that will be a prospect of benefit to all participants who otherwise wouldn't have any access.

So just as a recommendation that this is an important thing to have the sponsor work in coordination with ministries of countries who are faced with that dilemma.

DR. BADEN: Point well taken. I think we're not going to solve all the ethical challenges. I think the fact that there are 60,000 deaths annually, there's an unmet need that this can potentially contribute to solving. But the sponsor, with whatever product is emerging, is

going to have to struggle with this, and struggle with the communities that are relevant, that's in an ethically appropriate manner, and that's assumed. But how to define that will have to be defined 1 year, 5 years from now when the facts are available, but the ethics will have to be addressed in a very thoughtful way. But there clearly is an unmet need, and perhaps this can help address that in some small way.

We have to get to voting shortly, so I'm going to ask that comments be pithy, and then there may be a couple of pointed issues that I want us to address before we vote.

Dr. Burgess?

CAPT BURGESS: Hopefully a pithy question, but back to Dr. Follmann. I just want to clarify, when you were describing the 750 versus 750, you said double-blinded. I just want to ask the folks' thoughts about the importance of allocation masking in the context of a rabies post-exposure study.

DR. BADEN: That was one of the issues I was going to focus in on, so thank you.

Dr. Follmann, do you wish to comment?

DR. FOLLMANN: Just for the generic reasons, we like blinding, so the participant will know they got a blinded product as opposed to the new thing versus the reliable thing. I don't know the specific scenarios why that would cause necessarily a particular problem other than it's just good clinical trial practice. I would think it'd be relatively easy to blind in the study relative to like other things, I could imagine, but I really don't know how easy blinding would be.

CAPT BURGESS: I think it might actually be practically difficult in certain circumstances because of the volume of the product, for example, and you could get around that. But the question really is, from a statistical perspective, from an hypothesis testing perspective, is that important?

DR. FOLLMANN: I guess it's less important for mortality where it's harder to imagine how lack of blinding would have an impact. Maybe for safety it is more important. Maybe safety studies in controlled populations where it's easier to

administer, you could double-blind and maybe in the field less, so we are focusing on mortality. I don't want to be dogmatic and say it has to be double-blinded. I was just imagining that would be the gold standard, but there might be practical issues with it. But mortality as an endpoint is hard to see how it would be impacted.

DR. BADEN: Dr. Kartsonis, did you have a comment?

Others? Because I think a critical point that we're being asked is what do we think of the 750 and what do we think of the study design, and whether it's a double-blind or open-label, given that it's a mortality endpoint for the efficacy, not for the safety, because I think the safety will get much harder to understand in an open format.

Anyone have strong views on should there be a comparator or not? I think Dr. Kartsonis earlier said the value of a comparator is to deal with the noise of the situation, particularly if the exposure amount is so variable that it's going to be hard to know what the background should be.

DR. GRIPSHOVER: That's actually what I was going to -- why I had my card up to clarify is that what we're voting on, because I strongly think we should have a comparator because I think if there's an outbreak of more rabid animals, we don't want it to mess it up. So I definitely think the 750 should be in a comparator study.

So part of my question is, is that what we're going to be voting on? Question C, is that 750 a randomized trial of H/equine RIG versus our new drug? I guess that's for the FDA or not, if that's what they're asking us.

DR. BADEN: The way I'm hoping to frame the vote, and the agency can chime in, is do we, each of us, think that if the BLA package had a safety element and efficacy element, would that be adequate for approval? The safety element proposed has a thousand subjects or participants for safety, and the efficacy is 750, is what they're proposing.

If you think that this could be adequate, you're allowed to say it should be 1500; it should be 200; that this is a path that makes sense; the

numbers are too high or too low, as a sense of confidence for the initial approval, and then whether or not you think that would be adequate for first line or second line. And I apologize to the agency that that's not defined for the label, but I think it will be important for is this adequate efficacy and safety that one could imagine it being used.

Then whether it's in the label or in the practice guidelines, that will work itself out because the community will know the data. But would this be adequate for an approval with all of the caveats we've been discussing, and then we can always say there should be bigger numbers, and we can leave that to the postmarketing discussion, but adequacy for approval.

If no objections from the agency, I'll be framing the question that way for the group. And in your yes/no discussion, succinctly comment on safety adequate, bigger, smaller; efficacy adequate, bigger, smaller; first line, second line. If you say no, then add in what's missing that

would be critical for a BLA to be seriously considered. We're not getting to the vote just yet, but I've framed the question.

Dr. Ofotokun?

DR. OFOTOKUN: One thing. Should that be really a question for us rather than it should be for -- if we agree that this should go forward, then they should get their statistician and clinical trial designers to work out the appropriate number that is needed. I don't know if that should be a question that we should address.

DR. BADEN: Your point's well taken, which is any specific application will be predicated on the details of that application. What I think I hear from the agency in the document and the presentation is, is there a roadmap of what an approval could look like, and is there is a roadmap that could lead to an approval with 101 details associated with the specifics of the product and the advantages or disadvantages of the product, or is it impossible to even consider a path to approval?

That's what I'm hearing, is that is there a path to approval? Of course I don't see us advocating this is set in stone; this is the answer. For a generic product that doesn't have anything special of concern, would this be a reasonable path to say that we could see approval with all of the postmarketing?

So I think the follow-on to approval would be critical, but you have to at least get over that first bar and say are there enough data to consider that this is a path to approval, realizing 5 years from now, the details of the product will guide the discussion and any other new science that emerges.

But I hear that that's the guidance the agency's looking for because, otherwise, developers don't even know where to begin to think about what path do we take to even begin to develop. And there I think we do want to encourage the community to think about developing new therapies for diseases that I don't think we're satisfied are adequately addressed globally.

Other key discussion points? I know

Dr. Swaminathan -- I'm easily fooled by the misaligned cards. So are there other key discussions? If not, the points that I wanted to highlight I think were highlighted, but does anyone want to comment on the thousand participants is adequate safety? Anyone have other comments about the 750 is adequate efficacy for the BLA? Do we need any other pointed discussion on that? Because I agree with Dr. Follmann, I am glad that the agency put out a straw man there because it is arbitrary, but it does have a rationale that makes sense, given the state of the data in this space.

Dr. Siberry?

DR. SIBERRY: Just briefly since it came up before, yes, that thousand makes sense, but we should explicitly say it should include children and pregnant women, and those will come in after some preset number go through the safety study. So I just want to make sure that they're explicitly considered in the group who have safety data collected.

DR. BADEN: What I would ask is that the

question before us will be is this a roadmap that makes sense? Then if there are key considerations like that, add that in your footnote. If you vote yes, if you vote no, please explain why you think there's a key element missing. But that would be part of the -- and how much of that is in the BLA element versus how much of that is in the postmarketing, given the requirements for the BLA and how you can expose children without benefit.

So I want to be sensitive to other regulations that have to be thought about as data are being accrued, but ultimately that would be necessary.

So if there is no other discussion on those key elements of the proposal, then we can move to vote. The vote on this will be yes, a package with this kind of information, and you can give comments on higher or lower numbers or this is reasonable, and comments on the first line, second line; no, and why no?

So would a data package containing the following additional information be sufficient to

support submission of a U.S. BLA, comparable RVNA levels and vaccine interference with a mAb cocktail versus HRIG or ERIG in a clinical trial of rabies-exposed subjects; comparable safety profile of the mAb versus HRIG or ERIG in at least a thousand subjects or participants; lack of mortality in at least 750 participants with increased risk of exposure.

If yes, would the described data package support first-line indication for use as part of PEP or a second-line indication such as when HRIG is not available? If no, what other elements would you want for a BLA to be considered? So yes, no, abstain.

May we begin the voting?

(Voting.)

DR. BADEN: We are a consistent lot: 16, yes; zero, no; zero, abstaining; zero, no voting. We will start on the left with Dr. Swaminathan. We have limited time because we still need to discuss the postmarketing. We already touched on that. But if when you affirm the way you voted, if you

can give whatever key elements associated with the adjunct comments I mentioned, that would be appreciated.

DR. SWAMINATHAN: I voted yes. Should I answer this question about the first-line indication?

DR. BADEN: Yes.

DR. SWAMINATHAN: I would say that I would be in favor of it being for a second-line indication such as when HRIG is not available and also to have exclusions for high-risk cases and situations in which the efficacy may not be generalizable, based on differences from the study population versus the broad indication as a first-line therapy for all types of cases.

DR. BADEN: That was Dr. Swaminathan. Please state your name, and then your vote, and then the comment.

DR. SIBERRY: George Siberry. I voted yes. I'll just add that I think that the initial studies should make sure to strictly limit inclusion to those who present within 72 hours of a bite. When

there's a bite, that's the reason to keep things somewhat similar. After an initial phase, when enough data are collected within the context of this study in adults, it is absolutely ethically and regulatorily appropriate to include children, and I would also say to consider including pregnant women at that point.

Finally, I will re-express my skepticism that we get meaningful information from 750 people who don't die when they get the alternative, with the current standard of care. That comparison provides relatively little information. Thank you.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: I voted yes, and I actually do think we should have a randomized trial of the two groups. And I would actually encourage engagement of communities that are not accessing either the new product or the rabies immune globulin currently where there's obviously still a huge need since we have 60,000 people dying of rabies. Regarding the label, I would suggest that we include to use it where HRIG is not available

until we get further results in the postmarketing study.

DR. BADEN: Dr. Green?

DR. GREEN: Michael Green. I voted yes. I think there's a need to define whether the comparator group will receive HRIG versus ERIG, and what that might imply in terms of number of participants receiving each of these alternatives if one or both are used. I support the inclusion of 750 recipients of the monoclonal cocktail and 750 recipients of either HRIG, or ERIG, or a combination therein. I do feel that children and perhaps pregnant women should be included at some point after an interim safety analysis of the trial in exposed individuals and the prior normals prove the safety.

If the study is powered to affirm a 99.5 percent survival, I would approve it with a plan on the label as a second-line therapy when HRIG is not available in the United States, and I would want the label to actually include the reasoning behind this level of approval compared to the equivalent

first-line therapy. When we get the postmarketing studies and data, I would hope that this eventually might evolve to equivalency and an upgrade to a first-line indication. Thank you.

DR. BADEN: Dr. Weina?

DR. WEINA: Peter Weina. I voted yes, assuming my second crystal ball is working inside of my first crystal ball. I say that because I agree we need a pathway to be laid out for sponsors to move the thing forward, but the reality is that this is all assuming that the cell culture data, and then the animal challenged data, and the healthy individual data is absolutely pristine and everything looks absolutely beautiful and nice. But when we're sitting here or our counterparts are sitting here 10 years from now, actually listening to the actual presentation on it, they're going to look at it and say 750 subjects are so much variability. How can we just do it with 750 subjects? There's no way we can approve it, and everyone will vote no.

I would echo the issue that we need to have

on the label -- if this is a pathway that's going to go forward, that it's going to be for a second-line indication only if the HRIG is not available. Again, state actually clearly in the label why it's listed as a second line and why it's being approved at all. I think that would help with the approval for it.

DR. BADEN: As time is short, Lindsey Baden. I voted yes. I think that a thousand seems reasonable; 750 seems reasonable. I favor also the comparative trial with local standard in the international environment; and second line, based upon these data, required postmarketing, and then the postmarketing would allow us to elevate our confidence in its activity.

Dr. Clark?

DR. CLARK: Nina Clark. I voted yes. I also think using as many trials sites as possible, where RIG isn't given routinely, is the ideal. I accept the rationale for the numbers proposed for participants as assurance that a larger studies should be done, and then agree with the second-line

designation, particularly HRIG is unavailable until more data are available.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: I voted yes. I think I gave my reasons before. I think the thousand and the 750 randomized to a comparator is important. I think it should be used for a second-line indication when the HRIG is not available.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun. I voted yes for many of the reasons that have been expressed. I think the numbers 750 and thousand is set quite adequate. I also agree with the second-line designation until additional information is available. I would also reiterate that it will be important that as safety data becomes available, that we should enroll diverse population, women and children, older age group, so that we know how this drug works in these different population groups.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: Timothy Burgess. I voted yes. I concur with the proposed rationale for the

numbers and occur with the comments that have been articulated about encouraging the inclusion of a diversity of populations. I would favor a trial design that involved a comparison with local standard of care, and concur with second-line indication.

DR. BADEN: Dr. Porter?

DR. PORTER: Laura Porter. I agree with what has been said before. I voted yes. I believe that second-line application if HRIG is not available and also to be consistent with the local standard of care.

DR. BADEN: Dr. Baker?

DR. BAKER: Judith Baker. I voted yes. I concur with the previous comments regarding local trial, local standards, age diversity, pregnant women, children, and older ages.

DR. BADEN: Thank you. Dr. Harrist?

DR. HARRIST: Ally Harrist. I voted yes. The numbers seem reasonable to me. I agree with including a diverse population and think that it should be second line.

DR. BADEN: Dr. Ellison?

DR. ELLISON: James Ellison. I voted yes. I agree the 750/1000 is a good number. They should use a diverse population, including children and second line.

DR. BADEN: Dr. Moore?

DR. MOORE: I voted yes. This is Susan Moore. I agree it should use the local standards of post-exposure treatment, and I think it should exclude high-risk bites, exposures.

DR. BADEN: Dr. Brown?

DR. BROWN: Catherine Brown. I voted yes. I agree with the rationale behind the proposed numbers. I agree with having a local comparator group, range of ages and both genders, and approved for a second-line indication.

DR. BADEN: Thank you. So I think we have a lot of consensus in our comments. Some additional comments by individual members, but largely consensus that there is a path forward here.

The final discussion element is postmarketing studies. There is no vote associated

with this. It's just a discussion. We have about 10 or 15 minutes.

What are the key elements for postmarketing studies? If I heard everyone's tone properly, I think we all agree that that's a must, so it's a required element. The number put out there is 6,000. And the next phase, the 6,000 to get to 99.9 percent seems reasonable. It's a straw man, but it's a reasonable straw man. Again, the 250,000 in the other study is always more attractive, but one has to do it step-wise as you incrementally develop data.

What key elements in the postmarketing study would members of the committee think to be critical? Diversity, I'll put 6,000 out there cause that's proposed, seems reasonable to get to the 99.9 percent. What other elements should be considered in the postmarketing element?

Dr. Burgess?

CAPT BURGESS: I think for a U.S. BLA, no disagreement with the number for 6,000, but I think a key element should focus on assessment of

exposures in the United States because the licensure package is going to be based on effectively canine rabies. That to me heightens the importance of close attention to non-canine rabies potential exposures.

DR. BADEN: As part of that, I think it is very hard to capture the virus associated with an exposure because we can't even sort out if an exposure occurred. However, if there's a failure, one would be able to look at the failure very intensely to understand any potential relationship with the intervention.

CAPT BURGESS: But there's usually a clinical indication for the post-exposure prophylaxis, which would infer the likely --

DR. BADEN: Of course.

CAPT BURGESS: -- the seriousness, if the exposure occurred at all.

DR. BADEN: Correct. Absolutely.

Dr. Green?

DR. GREEN: A comment and a second comment. I think it would be hard to get many of those 6,000

in the United States if they label it as a second-line indicator unless we actually have a shortage. Should there be a shortage in the United States, we should definitely be very aggressive trying to capture those information.

Having said that, what we could do is if it's being used in geographic variable locations outside of the United States, whether it's Africa, India, the Philippines, et cetera, we should try to get diverse utilization outside of the United States to get a sense of range of its protectiveness.

I they should definitely -- in their post exposure, it's a good opportunity to look at the variances of age to see if it's difference in those that might be limited in the original study but getting a lot of kids, getting a lot of elder individuals, and if they haven't got very many pregnant women and it was used to look at it in pregnant women. So really, an opportunity to enhance our understanding of the areas that might have been more limited in the original trial.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: I think it's also an opportunity to look at how effective this product will be in individuals that are immunocompromised, which we have not really talked about. And there will be a broad range of immunocompromised individuals, particularly in a resource-limited setting that will be primarily HIV-infected individuals.

DR. BADEN: And in that setting, would you look at that as more of a healthy volunteer study versus a post-exposure study to make sure the kinetics of the intervention behave the same way in that population?

DR. OFOTOKUN: Because of the safety concern, it would be probably postmarketing people who really need it and then have an opportunity to really study whether it's effective and safe in that setting, rather than expose people who don't need it to a product that will show how they're going to react to it.

DR. BADEN: Because I think how well it

works in special populations --

DR. OFOTOKUN: Yes.

DR. BADEN: -- will be important.

Dr. Swaminathan?

DR. SWAMINATHAN: There are just a couple of issues that I see. One is that if it's marketed as labeled, which we pretty much agreed it would be a second-line indication, then the conclusions that can be drawn from postmarketing studies of that population will be limited by the fact that it will be a unique population where standard medical care is not available for either economic or political reasons. So it's going to be then given where HRIG is not available or current standard of care is not available.

Then the other --

DR. BADEN: Is that good or bad? I'm not sure I fully understand your comment.

DR. SWAMINATHAN: Well, for example, let's say that the characteristics of exposure and medical care, adequacy, and consistency of PEP may all be not representative of what would obtain

under better circumstances. So results could potentially be worse than under ideal circumstances, and that population may -- one would have to look at the data from such postmarketing studies with the realization that this is not a --

DR. BADEN: The generalizability. The population will have certain characteristics that are selected for, and that will have to be managed in the interpretation of the data.

DR. SWAMINATHAN: The other thing is -- and this has to do with what Dr. Green was talking about, is that short of a bat invasion in this country, it's unlikely that there will be much usage because there will not be a situation where HRIG is not available.

So I would think that even though there's a path forward that we've mapped here, that will be a very short path without much likelihood of at least immediate expansion into non-first-line indication populations.

DR. BADEN: The presumption there is that the U.S. is the primary space of interest.

DR. SWAMINATHAN: No. I'm just saying that the way this is mapped, it may never -- or it's difficult for me to envision a scenario where the postmarketing studies would provide enough additional further confirmation of its applicability in the U.S.

DR. BADEN: I guess I'm struggling with the issue of if one uses this intervention in high-risk individuals, wherever they are in the world, and the rabies breakthrough is very, very, very small, wouldn't that be reassuring, even though it's not a single U.S. person for argument's sake?

DR. SWAMINATHAN: Well, first of all, I'm not sure that -- I guess they would be high-risk people in places where the first-line therapy was not available.

DR. BADEN: What's driving my thinking is not that we can resolve it, but if I'm a sponsor, I would say there are 59,000 people who died this year with rabies. Let me figure out how to push this into those spaces where whatever is going on, those are untreated. And those 59,000 people are

not all the exposed. All the exposed is probably a million of which 59,000 were really exposed and died.

So that is not something we can solve, but I see that as a path for a sponsor to say there's a development path here because there's an unmet need. And if we're able to get into those spaces and show that it works, the 750 will be let's say in an RCT. The 6,000 may be uncontrolled. It's really a case series. But in the case series, if the characteristics are high enough risk, then might that be some evidence that there's activity? Then it all will depend on the adequacy of capturing failure, which is going to be a very tricky issue in a non-rigorous clinical trial.

DR. SWAMINATHAN: My concern isn't that -- I think the postmarketing follow-up, where it's given, under this labeling indication, will provide further confirmation of its safety and efficacy, and so forth. But it will not provide, at least not very soon, any evidence that that data on canine rabies in India applies to the type of

exposure and rabies that we have in this country.

DR. BADEN: No, that --

DR. SWAMINATHAN: Because, again, I say to you, you have been exposed by a bat. I can either give you HRIG or I can give you this other thing that works in other countries and other kinds of rabies, but we don't know how well it works with bat rabies.

DR. BADEN: But it's also very hard to interpret it in the U.S. data because we don't really understand any of the exposure. And the exposure is, I saw a bat. The exposure is incredibly variable, and I know in my state it wasn't even I saw bat; it's some kid brought a bat into school that was nailed on a board for show and tell, and was that an exposure?

So I think that it gets very hard to define exposure, and that was a complex discussion in our state.

Time is short. Yes?

DR. BELL: Sometimes things get used off label. Though we can't say that at the FDA, but

that's an opportunity for data. Like Dr. Harris brought up, maybe it's an option that's better than not having HRIG for some people.

DR. BADEN: Sure. I still am impressed with there's enough global need that you -- high quality data are out there to be had, in my view if I were a sponsor, because I see there are a lot of deaths. We can put that challenge on the sponsor to come up with a development plan that's convincing, but there's enough global substrate that one could imagine a development plan that could be, and sponsors are creative.

I'm sorry. Dr. Siberry?

DR. SIBERRY: We had some prior discussions about some 4 to 1 randomization in this step that confused me because my thought of this postmarketing is capturing information about use of the licensed drug in the real world. So I just wanted to confirm that this was not a plan for a randomized trial; that's one.

Then second, off-label use will absolutely happen. And if this is a tiny volume that people

like, and the bat nailed to the wall gets brought to the classroom, I'll bet you they'd much rather give that tiny volume to those 30 kids than the bigger volume.

So I think that our concern that a licensed product that's out there that has other characteristics that make it appealing won't get used may be a concern that's greater than reality. So I think the 6,000 good. We should be willing to count on information from global health settings, but I think, at least separately, we should also put a requirement to the sponsor of a minimum number of uses in the United States because I do think this is our opportunity to make sure we are collecting information about use in the United States.

DR. BADEN: But one could add to that that if it is approved and used, they can track use to infinity. There can be a higher resolution for an earlier number and a lower resolution, but again, 250,000 were tracked elsewhere, and there were no failures. I'm not sure I believe it, but it was

believable enough to lead to approval.

DR. SIBERRY: The fact is any case of rabies in the U.S. is going to get attention, so we will absolutely have --

DR. BADEN: But Dr. Green told us about a case of rabies that we didn't know was rabies until 18 months later when a transmission occurred. So I'm not sure --

MALE COMM MEMBER: [Inaudible - off mic] occurred at 18 months earlier.

DR. BADEN: No, but the person who died, we did not know was rabies. So there may well be rabies deaths that we don't know because it's a motor vehicle accident, and we're done.

Dr. Burgess?

CAPT BURGESS: I also had involvement in that case, and yes, the organ donor, the time from exposure to the donor's death was 18 months. And the time from organ receipt in the tragic transplant was ominously 18 months, and it was raccoon rabies, so that, yes, there are cryptogenic exposures and undiagosed cases.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: This gets to the issue of the postmarketing studies randomized or not. And I guess the way it's written, it is agnostic on that point. But I had thought we definitely had discussed randomization, and that's like at a 3 to 1 ratio, and I think that would be a preferred design to just looking at the 6,000.

I'm a little concerned about the risk, basically. We talked a lot about it; we don't know what kind of exposure there is, really; that's a big unknown. And having a control group here would help I guess deal with that unknown about are these really risky people are not.

For example, if we've got 6,000 people with head bites, would we really want to show 99.9 survival as the bar? Maybe it would be lower. That survival rate is really tied to historical data, which defines risk in a certain way that I guess you could -- or defines exposure in a conventional way. That rate is tied to that definition of exposure, and I would have more

comfort if we had a control group in the postmarketing study.

DR. BADEN: Other burning comments on postmarketing? Dr. Siberry, you're signaling me.

So I will conclude our discussion there. I don't think it's a conclusive discussion. I think the issue in the postmarketing will have to be determined based upon the data for the package, and the product, and the other features. There are some arguments for postmarketing having a control group, which means a much more organized study. For some number to increase the data, that will have to be gauged based upon the product and the product characteristics.

There will be potentially off-label use and other types of use that will be many other streams of data, and I think additional studies may be targeted studies at key risk groups, be they immunocompromised, or pregnant, or pediatric, that one can target to gain either data in the non-exposed healthy individual or in the exposure setting, and that would also be an important

discussion with the applicant at the time the product was being moved forward and given its characteristics.

Whatever the study is, 6,000 with a comparator component, it will then be well beyond that, and that one would want to capture data at different levels of granularity each step of the way given the concerns raised.

I think we've had a very long and extensive discussion despite an extremely short and concise set of presentations. So I would like to, again, thank the agency for positioning such a robust discussion with the way in which the data and the questions were presented.

What I would like to do is to see, before we adjourn, if the agency has any comments.

DR. MURRAY: Well, the feedback was beyond our dreams. We didn't expect to get this much consensus and maybe certainly not a unanimous vote, and just a high-level agreement even on the nuances. So we're very thankful for that and almost surprised.

Thank you for your excellent chairmanship in helping to navigate this process. It's a very difficult, complex topic, and you did an excellent job. Everybody had excellent feedback for us. Thank you so much.

DR. BADEN: Well, thank you. Other comments?

(No response.)

Adjournment

DR. BADEN: No. Thank you. And I'd like to thank the Committee for your tremendous effort, attention, and participation in the complex issues and in discussing them so thoroughly. We'll conclude today's meeting and remember to take all your belongings, and thank you. The meeting is now adjourned.

(Whereupon, at 4:36 p.m., the meeting was adjourned.)