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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

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Lauren Tesh Hotaki, PharmD, BCPS**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS**

9 **(Voting)**

10 **Lindsey R. Baden, MD**

11 *(Chairperson)*

12 Director of Clinical Research

13 Division of Infectious Diseases

14 Brigham and Women's Hospital

15 Director, Infectious Disease Service

16 Dana-Farber Cancer Institute

17 Associate Professor, Harvard Medical School

18 Boston, Massachusetts

19

20

21

22

1     **CAPT Timothy H. Burgess, MD, MPH, FACP**

2     Director

3     Infectious Disease Clinical Research Program

4     Preventative Medicine & Biostatistics

5     Uniformed Services University of the Health

6     Sciences

7     Bethesda, Maryland

8

9     **Nina M. Clark, MD**

10    Professor

11    Stritch School of Medicine

12    Clinical Division Director, Infectious Diseases

13    Director, Transplant Infectious Disease Program

14    Loyola Medical Center

15    Maywood, Illinois

16

17

18

19

20

21

22

1     **Dean A. Follmann, PhD**

2     Assistant Director of Biostatistics

3     Chief Biostatistics Research Branch

4     National Institute of Allergy and

5     Infectious Diseases

6     National Institutes of Health

7     Bethesda, Maryland

8  
9     **Michael Green, MD, MPH**

10    Professor of Pediatrics, Surgery and Clinical &

11    Translational Science

12    University of Pittsburgh School of Medicine

13    Division of Infectious Diseases

14    Director, Antimicrobial Stewardship & Infection

15    Prevention

16    Co-Director, Transplant Infectious Diseases

17    Children's Hospital of Pittsburgh

18    Pittsburgh, Pennsylvania

19

20

21

22

1     **Barbara M. Gripshover, MD**

2     Associate Professor of Medicine

3     University Hospitals Cleveland Medical Center

4     Case Western Reserve University

5     Division of Infectious Diseases and HIV Medicine

6     Cleveland, Ohio

7

8     **Ighovwerha Ofotokun, MD, MSc**

9     Professor of Medicine

10    Division of Infectious Diseases

11    Department of Medicine

12    Emory University School of Medicine

13    Atlanta, Georgia

14

15    **George K. Siberry, MD, MPH**

16    Medical Officer

17    Adult Clinical Branch, Office of HIV/AIDS

18    S/GAC Senior Technical Advisor for Pediatrics

19    U.S. Agency for International Development

20    Arlington, Virginia

21

22

1     **Sankar Swaminathan, MD**

2     Professor and Chief, Division of Infectious

3     Diseases

4     Department of Internal Medicine

5     University of Utah School of Medicine

6     Salt Lake City, Utah

7

8     **Peter Joseph Weina, PhD, MD**

9     Colonel, Medical Corps, US Army

10    Branch Chief, Research Regulatory Oversight Office

11    Office of the Under Secretary of Defense

12    (Personnel and Readiness)

13    Defense Health Headquarters

14    Falls Church, Virginia

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1       **ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS**

2       **(Non-Voting)**

3       **Nicholas A. Kartsonis, MD**

4       *(Industry Representative)*

5       Sr. Vice President

6       Infectious Diseases & Vaccines, Clinical Research

7       Merck Research Laboratories

8       North Wales, Pennsylvania

9

10       **TEMPORARY MEMBERS (Voting)**

11       **Judith Baker, DrPH, MHSA**

12       *(Consumer Representative)*

13       Public Health Director

14       Western States Regional Hemophilia Network

15       Pacific Sickle Cell Regional Collaborative

16       Center for Inherited Blood Disorders

17       Adjunct Assistant Professor

18       UCLA-Division of Pediatric Hematology/Oncology

19       Los Angeles, California

20

21

22

1     **Catherine M. Brown, DVM, MSc, MPH**  
2     State Epidemiologist and State Public Health  
3     Veterinarian  
4     Bureau of Infectious Disease and Laboratory  
5     Sciences  
6     Massachusetts Department of Public Health  
7     National Association of State Public Health  
8     Veterinarian's Compendium of Animal Rabies  
9     Control and Prevention, Co-chair  
10    Boston, Massachusetts

11  
12    **James A. Ellison, PhD**  
13    *(speaker and temporary member)*  
14    Microbiologist  
15    Poxvirus and Rabies Branch  
16    Division of High-Consequence Pathogens and  
17    Pathology  
18    National Center for Emerging and Zoonotic  
19    Infectious Diseases  
20    Centers for Disease Control and Prevention  
21    Atlanta, Georgia

22

1     **Alexia Harrist, MD, PhD**

2     State Health Officer and State Epidemiologist

3     Chief, Public Health Sciences Section

4     Public Health Division

5     Wyoming Department of Health

6     Cheyenne, Wyoming

7

8     **Susan M. Moore, PhD, MS, HCLD (ABB), MT (ASCP) SBB**

9     Clinical Assistant Professor/Rabies Laboratory

10    Director

11    Kansas State Veterinary Diagnostic Laboratory

12    College of Veterinary Medicine

13    Kansas State University

14    Manhattan, Kansas

15

16    **Laura D. Porter, MD**

17    *(Patient Representative)*

18    Cheverly, Maryland

19

20

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22

1       **FDA PARTICIPANTS (Non-Voting)**

2       **John Farley, MD, MPH**

3       Deputy Director

4       Office of Antimicrobial Products (OAP)

5       Office of New Drugs (OND)

6       CDER, FDA

7

8       **Debra Birnkrant, MD**

9       Director

10      Division of Antiviral Products (DAVP)

11      OAP, OND, CDER, FDA

12

13      **Jeffrey Murray, MD, MPH**

14      Deputy Director

15      DAVP, OAP, OND, CDER, FDA

16

17      **Stephanie Troy, MD**

18      Medical Officer

19      DAVP, OAP, OND, CDER, FDA

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**Tanvir Bell, MD, FACP, FIDSA**

Medical Officer

DAVP, OAP, OND, CDER, FDA

**Damon Deming, PhD**

Clinical Virology Reviewer

DAVP, OAP, OND, CDER, FDA

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P R O C E E D I N G S

(8:30 a.m.)

**Call to Order**

**Introduction of Committee**

1 DR. BADEN: Good morning. I'd like to call  
2 this meeting to order. I would first like to  
3 remind everyone to please silence your cell phones,  
4 smartphones, and any other devices if you've not  
5 already done so. I would also like to identify the  
6 FDA press contact, Allison Hunt. If you are  
7 present, please stand. Allison will be joining us  
8 later.  
9

10 My name is Dr. Lindsey Baden. I'm the  
11 chairperson of the Antimicrobial Drugs Advisory  
12 Committee, and I will be chairing this meeting. I  
13 will now call this meeting to order. We'll start  
14 by going around the table and introduce ourselves.  
15 We'll start with the FDA to the far left.  
16

17 DR. FARLEY: Good morning. John Farley,  
18 deputy director of the Office of Antimicrobial  
19 Products, CDER, FDA.  
20

21 DR. BIRNKRANT: Good morning. Debbie  
22

1 Birnkrant, director of Division of Antiviral  
2 Products, FDA.

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

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

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

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

11 DR. SWAMINATHAN: Sankar Swaminathan,  
12 University of Utah.

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

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

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

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

1 Undersecretary of Defense.

2 DR. HOTAKI: Lauren Hotaki, designated  
3 federal officer.

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

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

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

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

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

19 DR. PORTER: Laura Porter, patient  
20 representative.

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

1 Orange, California and UCLA School of Medicine.

2 I'm here today as the consumer representative.

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

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

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

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

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

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

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

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

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

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

1                                   **Conflict of Interest Statement**

2                   DR. HOTAKI:   The Food and Drug  
3           Administration is convening today's meeting of the  
4           Antimicrobial Drugs Advisory Committee under the  
5           authority of the Federal Advisory Committee Act of  
6           1972.   With the exception of the industry  
7           representative, all members and temporary voting  
8           members of the committee are special government  
9           employees or regular federal employees from other  
10          agencies and are subject to federal conflict of  
11          interest laws and regulations.

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

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

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

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

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

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

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

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

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

12 Thank you.

13           DR. BADEN: Thank you.

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

16           **FDA Opening Remarks - Jeffrey Murray**

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

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

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

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

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

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

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

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

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

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

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

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

9 DR. BADEN: Thank you.

10 Dr. Bell?

11 **FDA Presentation - Tanvir Bell**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 This is, again, those three components of

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

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

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

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

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

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

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

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

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

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

1 of rabies infection.

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

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

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

22 There are limitations to rabies

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

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

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

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

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

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

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

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

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

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

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

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

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

1 talks.

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

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

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

22 There is a monoclonal antibody that's

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

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

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

1 preparing this advisory committee talk and  
2 workshop.

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

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

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

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

5 Dr. Deming?

6 **FDA Presentation - Damon Deming**

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

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

1           Ideally, any monoclonal antibody replacement  
2 to RIG would be able to neutralize any circulating  
3 virus at least as well as a polyclonal product.

4 But that actually is a challenging goal; it might  
5 be a challenging goal to achieve.

6           The ancestor to contemporary rabies was  
7 believed to have spilled over from a bat host some  
8 900 to 1500 years ago, and since that time it's  
9 jumped into several other hosts, and adapting as it  
10 goes along. Over time and as it adapts to new  
11 hosts, it accumulates several changes across its  
12 genome, including against the glycoprotein, which  
13 as Dr. Bell mentioned is the only extracellular  
14 protein and is the target for all neutralizing  
15 antibodies.

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

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

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

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

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

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

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

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

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

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

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

1 one of several dilutions of an antibody.

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

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

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

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

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

19 In this example, the reference neutralized  
20 50 percent of the wells at a 4-fold lower dilution,  
21 meaning that it was 4-fold more potent. If the  
22 referenced antibody has an EC50 value of 2 IU per

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

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

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

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

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

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

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

1 10,000-fold above the CC50 value. So we predict  
2 that it has a pretty high neutralization potential  
3 against that isolate.

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

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

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

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

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

1 gaps in coverage, which we would find concerning.

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

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

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

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

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

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

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

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

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

7               DR. BADEN: Dr. Troy?

8               DR. ELLISON: Yes. Thank you.

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

10              DR. BADEN: Thank you, Dr. Deming.

11              Dr. Ellison?

12                       **Speaker Presentation - Dr. Ellison**

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

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

1 thus experimentally passing rabies.

2 Pasteur really built on that in the early  
3 1800s and demonstrated that it could be transmitted  
4 from animal to animal using the rabbit model, and  
5 what this did was it really set a foundation for  
6 future studies in pathogenesis diagnosis and  
7 eventually vaccine production.

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

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

1 has been learned from experimental animal models.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 These are RNA viruses.

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

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

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

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

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

17               DR. BADEN: Thank you, Dr. Ellison.

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

22               We'll resume in 15 minutes. I will remind

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

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

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

7 **FDA Presentation - Stephanie Troy**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So there's usually some amount of vaccine

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

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

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

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

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

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

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

22 Even though the little red line is very

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

8 Adding to the challenge the uncertainty  
9 regarding these estimates, the 99 percent and the  
10 99.9 percent, it's probably greater than the  
11 contribution of the RIG component itself because  
12 these estimates are based on field trials and  
13 observational studies using different vaccines,  
14 different schedules, different RIG amongst subjects  
15 with different risk for rabies development.

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

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

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

15 The time interval between the exposure and  
16 the administration of PEP is very important. It's  
17 universally recommended that this should be done as  
18 soon as possible, but the definition of prompt is  
19 not clear, so some studies define it as less than  
20 24 hours. Others have gone out to 7 days, and that  
21 can make a big difference in the risk of developing  
22 rabies.

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

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

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

1 because too many subjects would be required.

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

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

21 The trials that we pulled went back to the  
22 1950s, used different varieties of vaccines,

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

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

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

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

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

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

1 could say that the survival rate is greater than  
2 99.5 percent.

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

12 Now for this, we thought 0.01 percent was a  
13 reasonable estimate based on the observational data  
14 in the Philippines, but it could also be a higher  
15 rate. And if it's a higher rate, the sample sizes  
16 go up quite a bit. The third column is the sample  
17 size is required to have at least 80 percent power  
18 and these were done in multiples of 500. So using  
19 this table, if you wanted to rule out a 0.1 percent  
20 mortality, in other words, if you wanted to  
21 demonstrate that the survival rate was greater than  
22 99.9 percent, you would have to enroll 6,000

1 subjects to have at least 80 percent power.

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

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

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

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

9 The data we have on how feasible it might be  
10 is there was a rabies monoclonal antibody trial in  
11 India, and that took over 2 years to enroll 200  
12 subjects as Dr. Bell mentioned earlier.

13 Optimistically, there is now a report that a study  
14 with 4,000 subjects is planned in the same country  
15 where this monoclonal antibody is approved. So at  
16 least in the postmarketing setting, it's possible  
17 that larger amounts of patients could be enrolled.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 For postmarketing, our proposal is 6,000

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

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

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

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

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

### 7 **Clarifying Questions**

8 DR. BADEN: Thank you, Dr. Troy.

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

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

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

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

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

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

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

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

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

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

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

1 way to demonstrate activity at least in those  
2 models?

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

14 What was the second part of your question?

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

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

22 DR. BADEN: And the hamster and the dog

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

3 DR. ELLISON: Yes, in my opinion.

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

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

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

17 What was the second part?

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

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

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

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

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

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

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

22 Dr. Moore?

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

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

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

1 seroconvert, and survive.

2 DR. BADEN: Dr. Green?

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

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

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

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

3 DR. BADEN: Dr. Burgess?

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

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

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

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

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

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

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

22               DR. ELLISON:  I don't think I quite

1 understand your question.

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

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

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

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

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

22 How would we establish that the antibody to

1 the glycoprotein is truly the key in the human  
2 model?

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

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

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

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

20 DR. BADEN: Dr. Deming?

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

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

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

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

12 (Crosstalk.)

13 DR. ELLISON: Correct.

14 DR. DEMING: -- Fc-effector functions.

15 (Crosstalk.)

16 DR. BADEN: Dr. Moore?

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

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

6 DR. BADEN: Dr. Follmann?

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

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

22 So I was wondering if in the hamster model

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

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

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

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

19 DR. ELLISON: Correct.

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

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

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

7 DR. ELLISON: Yes.

8 DR. BADEN: -- or could be.

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

11 DR. BADEN: Dr. Moore?

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

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

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

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

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

20 DR. BADEN: Dr. Weina?

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

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

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

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

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

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

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

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

18 DR. BADEN: Dr. Clark?

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

22 DR. ELLISON: When it's inoculated

1 experimentally, it results in an abortive  
2 infection.

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

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

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

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

4 DR. BADEN: Dr. Gripshover?

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

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

10 DR. GRIPSHOVER: Okay. Great. Thanks.

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

13 DR. BADEN: Dr. Bell?

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

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

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

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

11 DR. BADEN: Follow-on?

12 MALE VOICE: No, no.

13 DR. BADEN: Then Dr. Ofotokun?

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

1 immunoglobulins.

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

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

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

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

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

1 when you have the clinical disease.

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

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

14 DR. BADEN: Dr. Follmann?

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

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

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

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

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

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

6 (Crosstalk.)

7 DR. FOLLMANN: I was curious about that.

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

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

12 DR. FOLLMANN: So this would be in animals.

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

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

17 (Laughter.)

18 DR. BELL: That's right.

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

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

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

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

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

15             DR. BADEN: Dr. Green?

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

1 looking at pace over time?

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

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

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

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

22 DR. BADEN: Dr. Ofotokun?

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

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

16 DR. BADEN: Dr. Bell?

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

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

4 DR. BADEN: Follow on?

5 (No response.)

6 DR. BADEN: Dr. Ellison, thank you.

7 DR. ELLISON: Thank you.

8 DR. BADEN: You can join us at the table.

9 We may still have more questions for you, and you  
10 will have to jump between your visages.

11 DR. BADEN: Dr. Gripshover?

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

19 DR. ELLISON: Typically, with the studies  
20 that I'm familiar with, they give it at 6 hours or  
21 24 hours post-infection. Your question would be,  
22 so once it already gets to the spinal cord, say the

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

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

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

20 DR. BADEN: Dr. Porter?

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

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

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

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

22 DR. BELL: So I looked up the HRIG approval

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

9 Robin, can you add more?

10 DR. SCOTT: I would say the shelf life of  
11 HRIG, I believe, is 36 months if I'm not mistaken,  
12 and that's 4 to 8 degrees. However, there are a  
13 lot of stability studies that are done at  
14 accelerated conditions, and perhaps that's what  
15 you're referring to; for example, a temperature of  
16 42 or even 60 degrees.

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

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

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

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

12 DR. SCOTT: Will you repeat the question?

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

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

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

4 DR. BADEN: A procedural issue --

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

6 DR. BADEN: Thank you, Dr. Scott.

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

12 (Laughter.)

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

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

1 prophylaxis failure.

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

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

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

15 DR. BADEN: Dr. Harrist?

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

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

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

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

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

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

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

1 antibody going to address that issue?

2 DR. BADEN: Dr. Troy?

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

4 DR. BADEN: Dr. Siberry?

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

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

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

1 least some U.S. sites.

2 DR. BADEN: Dr. Clark?

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

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

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

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

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

4 DR. TROY: I think some of the barriers were  
5 unique, and it was the first trial of a clinical  
6 trial in rabies-exposed subjects of a monoclonal  
7 antibody. That was done at 5 sites. I do think  
8 it's optimistic that they're planning a trial in  
9 4,000 subjects. They must think it's more likely  
10 now; I mean, more possible now to do higher  
11 numbers.

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

19 DR. BADEN: Dr. Baker?

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

1 overseas to address some of the feasibility issues?

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

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

22 All clinical trials, once they came in as

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

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

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

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

14 DR. BADEN: With thousands enrolled.

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

1 DR. BADEN: Dr. Green?

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

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

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

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

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

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

11 Is that right?

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

22 DR. BADEN: There are 6 people who have

1 claimed follow-on. Dr. Follmann?

2 DR. FOLLMANN: My follow-on is a little  
3 different than -- well, it's a follow-on from five  
4 minutes ago. I was interested in the -- this  
5 would be for Dr. Bell or Dr. Troy. It's about the  
6 200-person trial that was conducted in India and  
7 also the 4,000-person trial.

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

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

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

17 DR. BELL: HRIG, yes.

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

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

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

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

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

17 DR. TROY: Yes.

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

19 DR. TROY: Yes.

20 DR. FOLLMANN: The final thing, the  
21 4,000-person trial I guess is similar kinds of  
22 studies randomized to monoclonal versus HRIG, each

1 RIG?

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

6 DR. FOLLMANN: Okay. Thanks.

7 DR. BADEN: Dr. Ofotokun?

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

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

22 DR. TROY: Ideally, these studies could be

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

12 DR. BADEN: Dr. Gripshover?

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

22 DR. BADEN: Dr. Birnkrant?

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

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

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

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

4 DR. BADEN: But this is in the back drop of  
5 59,000 deaths a year from rabies.

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

11 DR. BADEN: Dr Gripshover?

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

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

1 right now?

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

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

18 DR. BADEN: Definitely challenging.

19 Dr. Birnkrant?

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

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

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

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

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

19               DR. BADEN: Dr. Swaminathan?

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

1 considered that important, such as the fact that  
2 cost isn't really the thing that's being considered  
3 here. We have existing treatment that is virtually  
4 100 percent effective.

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

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

21 DR. BADEN: Dr. Troy?

22 DR. TROY: I can start commenting on that.

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

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

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

1 way.

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

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

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

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

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

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

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

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

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

3 DR. HARRIST: Yes.

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

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

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

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

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

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

13 DR. BADEN: Dr. Brown?

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

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

1 concentration that would allow for a smaller volume  
2 for infiltration?

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

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

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

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

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

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

1 intramuscular injection?

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

4 DR. BADEN: Dr. Moore?

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

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

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

22 DR. BADEN: Please mention your name as

1 well, for the record.

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

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

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

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

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

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

19 DR. BADEN: Dr. Moore?

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

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

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

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

22           Given you know the epitope specificity of

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

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

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

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

1 work out and validate the assays using all of  
2 those.

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

9 Will you please state your name for the  
10 record?

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

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

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

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

10 DR. BADEN: I see.

11 Dr. Ellison?

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

1 DR. BADEN: Dr. Moore?

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

11 DR. BADEN: Thank you. Dr. Swaminathan?

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

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

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

7 DR. SWAMINATHAN: So then the interference  
8 could be fairly complex where you couldn't just  
9 sort of look at the differential response to  
10 different epitopes to determine whether it  
11 was -- you said that creative methods might be  
12 needed if the neutralizing titers are greater than  
13 0.5, and these are hypothetical examples. But in  
14 the studies, what has the level at, say, day 14  
15 from vaccine alone been with monoclonals?

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

1 and the monoclonal antibody alone got more than  
2 0.5, then a measure at day 14 of 0.5 wouldn't  
3 measure that. But there are ways we could detect  
4 the vaccine interference in that situation, too,  
5 that were in the backgrounder.

6 DR. BADEN: Dr. Moore?

7 DR. MOORE: Yes?

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

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

11 DR. BADEN: Dr. Harrist?

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

14 DR. BADEN: Moving to a different line of  
15 questioning, one of the challenges presented  
16 earlier has to do with the diversity of the rabies  
17 virus that infects humans, and should this be  
18 2 monoclonals, or 3 monoclonals, and which  
19 epitopes?

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

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

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

12 DR. BADEN: Well, what I'm getting at is we  
13 do have a panel in that we have strains that are  
14 known to have infected humans. And we take the  
15 most diverse of those strains, and then we  
16 rationally -- I guess what I'm getting at is there  
17 so much diversity that you wouldn't be able to get  
18 2 or 3 monoclonals because what's already known is  
19 too much diversity, or given what's known, one  
20 could imagine a manageable number of monoclonals  
21 that would have the desired coverage?

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

1 necessarily take more than 2 or 3.

2 DR. BADEN: Dr. Green?

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

9 DR. BADEN: Dr. Troy?

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

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

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

1 a whole working group at the World Health  
2 Organization to discuss this, and they came up with  
3 2 because they thought 2 would be adequate, 2 or  
4 more. I can't go into more details than that.

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

10 DR. BADEN: And there are many challenges  
11 with deciding what to go forward with, but it  
12 sounds like conceptually in an in vitro  
13 bioinformatic way, then with cell culture, we could  
14 at least imagine data which says here are 2 or  
15 3 monoclonals that have activity against the known  
16 circulating human disease-causing strains.

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

20 Dr. Moore?

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

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

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

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

20 DR. BADEN: Dr. Siberry?

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

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

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

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

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

20 DR. SIBERRY: Yes, failure.

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

1 DR. BADEN: Dr. Follmann?

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

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

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

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

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

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

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

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

20 Dr. Clark?

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

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

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

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

14 DR. BADEN: Dr. Burgess?

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

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

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

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

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

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

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

11          DR. BADEN: A follow-on?

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

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

22          DR. DEMING: Palivizumab for RSV.

1 DR. OFOTOKUN: For RSV?

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

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

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

9 (Laughter.)

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

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

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

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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)**

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

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

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

22 DR. CLARK: [Inaudible - off mic].

1 DR. BADEN: Excellent. Dr Weina?

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

4 (Laughter.)

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

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

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

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

5           So my question was the same thing with this.  
6 Have we really teased out the three different  
7 aspects of the post-exposure prophylaxis in which  
8 we've looked at -- how it was presented is  
9 99.9 percent effective. And if we add the  
10 rip [ph] -- thank you. Geez, my brain froze there  
11 for a second. When we added the RIP to it, we add  
12 a tiny little bit more efficacy to it.

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

22           It would seem to me that those would be very

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

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

16                DR. BADEN: Dr. Moore?

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

1 in the Syrian hamster model at all.

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

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

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

13 DR. WEINA: And is that uniformly like  
14 99 percent, or is it 75 percent?

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

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

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

4 DR. BADEN: In that model.

5 DR. DEMING: In that model.

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

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

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

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

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

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

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

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

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

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

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

6 Dr. Green?

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

16 The reason I think about this is that I  
17 chaired the disease transmission advisory committee  
18 at UNOS when the human-to-human transmission  
19 occurred, and that recipient died somewhere around  
20 18 months after getting an organ transplant from an  
21 index case or a donor that died of rabies. We were  
22 all fascinated and couldn't understand why an

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

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

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

18 DR. BADEN: Dr. Siberry?

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

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

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

10           DR. BADEN: Dr. Follmann?

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

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

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

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

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

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

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

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

10 DR. BADEN: Dr. Swaminathan?

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

13 DR. BADEN: Go ahead.

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

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

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

11 DR. BELL: You're right. And I bring back  
12 Dr. Troy's graph where the uncertainty amongst that  
13 99 percent with the yellow bars is there.  
14 Unfortunately, that's inherent in this disease  
15 process. The inoculum of the virus isn't always  
16 known and the type of bite. There's just a lot of  
17 variability in a lot of things we probably wouldn't  
18 be able to quantify with this condition.

19 DR. BADEN: Dr. Clark?

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

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

4 DR. BADEN: Dr. Clark?

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

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

12 Dr. Follmann?

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

1 effect the antibody had or didn't have.

2 DR. BADEN: Dr. Swaminathan?

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

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

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

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

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

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

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

1       neutralized factor?

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

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

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

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

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

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

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

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

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

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

16 DR. BADEN: Dr. Green?

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

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

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

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

22 DR. BADEN: Dealer's choice. Dr

1 Swaminathan?

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

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

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

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

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

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

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

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

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

14 Can you comment?

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

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

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

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

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

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

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

5 DR. BADEN: And the other two were bat?

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

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

10 DR. ELLISON: It was about the cryptic  
11 exposure.

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

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

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

10 DR. BADEN: What were the serologic  
11 measures?

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

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

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

1 total, correct?

2 DR. TROY: Yes.

3 DR. GREEN: Thank you.

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

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

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

1 DR. SCOTT: Yes, to a licensed HRIG.

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

3 DR. SCOTT: We have Imogam and HyperRAB.

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

6 DR. SCOTT: Yes.

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

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

11 DR. BADEN: Dr. Follmann?

12 DR. FOLLMANN: It's not a --

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

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

1 mAb, and then 250 people I guess getting HRIG.

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

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

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

17 DR. TROY: Yes.

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

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

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

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

14 DR. TROY: Safety, the main thing --  
15 (Crosstalk.)

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

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

22 DR. FOLLMANN: Okay. And the same thing I

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

3 DR. TROY: Yes, that is correct.

4 DR. FOLLMANN: Thanks.

5 DR. BADEN: Please, Dr. Siberry?

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

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

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

4 DR. SIBERRY: I just think we should  
5 separate them, the objectives. If there's short  
6 term safety and serologic objectives that require  
7 smaller numbers, that should be thought about what  
8 you'd need for that. If you tell me that you'll  
9 get meaningful information about a mortality  
10 difference by having 750 per arm, and you're the  
11 expert, help me understand. But again, I think  
12 we'd be looking for the number of deaths in those  
13 750 mAb recipients almost regardless of what  
14 happened in the 750 other recipients.

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

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

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

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

12 DR. BADEN: Debate is good.

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

15 DR. FOLLMANN: Oh, yeah.

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

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

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

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

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

16 DR. FOLLMANN: Right.

17 DR. SIBERRY: So it's a little different  
18 from a trial design when you're expecting say 10 to  
19 20 deaths per arm, and you really want to  
20 understand this. Again, you have more expertise in  
21 this, but when the expectation is zero in each of  
22 these arms, I'm not sure how much more you're

1       gaining by having --

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

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

14              DR. BAKER:  [Inaudible - off mic].

15              DR. BADEN:  Okay.  Then Dr. Kartsonis?

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

20              DR. BADEN:  Comparator.

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

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

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

16 DR. BADEN: Dr. Weina?

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

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

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

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

1 double-edge sword.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 What do you think?

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

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

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

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

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

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

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

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

3 Dr. Clark?

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

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

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

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

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

3 DR. BADEN: Dr. Farley?

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

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

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

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

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

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

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

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

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

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

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

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

19 DR. TROY: Yes.

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

22 DR. BELL: Obviously, the more proof would

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

4 DR. BADEN: Dr. Green?

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

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

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

5 DR. BADEN: I think Dr. Ellison --

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

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

20 DR. BADEN: Very challenging for study  
21 design.

22 Dr. Swaminathan?

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

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

15 DR. BADEN: Twenty per year, confirmed.

16 DR. BELL: That they get the heads.

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

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

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

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

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

11 DR. BADEN: Dr. Weina?

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

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

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

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

8               (No response.)

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

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

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

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

4 We have some products that have lasted more  
5 than 15 years that are lyophilized. This would be  
6 the coral snake antivenom, for example, which is  
7 used in Florida and hasn't been manufactured for  
8 some time, but still is licensed. I imagine the  
9 same may be the case for monoclonal antibodies. I  
10 just don't know.

11 **Questions to the Committee and Discussion**

12 DR. BADEN: Thank you. We will now proceed  
13 with the questions to the committee and panel  
14 discussions. I'd like to remind public observers  
15 that while this meeting is open for public  
16 observation, public attendees may not participate  
17 except at the specific request of the panel.

18 We will be using an electronic voting system  
19 for this meeting. I'll go through the procedure,  
20 and then we will open the discussion. We'll be  
21 using the electronic voting system. Once we begin  
22 the vote, the buttons will start flashing and will

1 continue to flash even after you've entered your  
2 vote. Please press the button firmly that  
3 corresponds to your vote. If you're unsure of your  
4 vote or you wish to change your vote, you may press  
5 the corresponding button until the vote is closed.

6 After everyone has completed their vote, the  
7 vote will be locked in. The vote will then be  
8 displayed on the screen. The DFO will read the  
9 vote from the screen into the record. Next, we'll  
10 go around the room, and each individual who voted  
11 will state their name and vote in the record. You  
12 can also state the reason you voted as you did if  
13 you want to. We'll continue in the same manner  
14 until all questions have been answered.

15 Now, this is a bit of an unusual meeting in  
16 that there's actually greater interest in the  
17 discussion of the challenge before us and before  
18 the agency and the community as we try to advance a  
19 product in this space. The agency would like us to  
20 discuss a little bit of the issues amongst the  
21 members, as we've already started to in the  
22 clarifying questions, to better illuminate the

1 challenges and what would be key elements of a path  
2 forward. 1 is the preamble to the vote in 2; 3 is  
3 the preamble to the vote in 4; and 5 will be the  
4 epilogue.

5 The first question, which really is more of  
6 a discussion, is what information is needed to  
7 support trials in rabies-exposed individuals?  
8 Please discuss any recommendations concerning the  
9 data required prior to evaluating a monoclonal  
10 antibody cocktail in place of RIG in clinical  
11 trials and rabies-exposed subjects?

12 What will occur when we vote is do we think  
13 there's a path forward, and then what would the key  
14 elements be to the path forward. But the  
15 discussion question on the floor is what is needed  
16 to move mAb forward in the context of RIG, and the  
17 floor is open to discussion.

18 Dr. Swaminathan?

19 DR. SWAMINATHAN: I think the animal  
20 challenge studies that support this should have  
21 relevance to the strains that circulate in areas  
22 where the vaccine might be applied. More than one,

1 perhaps, animal model might be required so that  
2 there's adequate coverage that the disease would be  
3 high enough penetrance in the model, so that the  
4 vaccine efficacy in that model would be generally  
5 applicable to the entire human clinical spectrum  
6 for which this product might be used more.

7 DR. BADEN: Dr. Weina? I think there's a  
8 lot of interest, and we'll work our way through  
9 everyone.

10 DR. WEINA: Again, my comments are on the  
11 animal challenge studies as well. Just  
12 demonstrating survivor benefit, as I've alluded to  
13 earlier, I think we really need to focus just on  
14 comparing the currently used HRIG with the  
15 monoclonal antibody alone, not with the vaccine, in  
16 the animal model, looking at mortality but  
17 measuring it after the animal has been challenged  
18 at time zero, and at time 6, and at time 12, and  
19 out several days to kind of get an idea of the  
20 comparison of the monoclonal antibody to the HRIG;  
21 and if the time period stretched out, if that has  
22 any influence at all, and a complete head to head

1 with the monoclonal antibody.

2 I think we're going to get enough from the  
3 healthy volunteers to see the issue of interference  
4 and everything else, that you don't have to do that  
5 in the animal models, but I think the animal models  
6 really have to focus on that monoclonal antibody,  
7 either by itself or in combination as the cocktail  
8 with a head to head on the HRIG.

9 DR. BADEN: I'm going to take chair's  
10 prerogative and organize the discussion a little  
11 bit, because I think the potential for us to go in  
12 many different directions is very high since the  
13 data are so rich. What I'd like to do is to  
14 structure the discussion in four part, utilizing  
15 what has been proposed to us.

16 The first part of the discussion will be  
17 what's needed in vitro, and we should all comment  
18 on what we think will strengthen the in vitro  
19 portfolio. The next will build on the animal  
20 concept. The next will be the human studies in the  
21 non-exposed and then the human studies in the  
22 exposed cause. I think we'll have a stronger set

1 of information to the agency if our collective  
2 comments and discussion are thematic.

3           So I agree with Dr. Weina's comment, but we  
4 will continue that discussion when we go to the  
5 animal part. I think the in vitro part may be  
6 relatively straightforward, and I will start by  
7 saying in the in vitro part, I think there needs to  
8 be a clear understanding of the globally  
9 circulating strains, old and new world, that have  
10 caused human disease, which includes acquiring more  
11 strains if there aren't adequate strain  
12 representation from key regions.

13           I accept the comments from Dr. Ellison that  
14 there may be more strains identified than have  
15 caused human disease, and we should have a  
16 preference to those that cause human disease. We  
17 should in the in vitro assays know which are  
18 neutralization, easy or hard, and make sure that we  
19 have a spectrum -- both genomically, we know the  
20 conserve nature of the epitopes of interest, and  
21 in vitro understand the resistance profile so that  
22 the monoclonals can be selected that have a strong

1 rationale that they're active against the known  
2 circulating strains genomically and the known  
3 circulating strains in vitro from a neutralization  
4 standpoint.

5           That would be predicate data that one would  
6 then, in the animal experiments, build on. But I  
7 think that would be an initial way to comprise what  
8 the monoclonal should look like, and whether it's a  
9 2 complement or a 3 complement, there can be a  
10 rationale for the complementary antibodies for the  
11 epitopes as well as the global strain diversity.  
12 Then one can do many in vivo studies to  
13 characterize the monoclonals with the known viruses  
14 to reassure ourselves that it has the spectrum of  
15 interest.

16           Dr. Ellison, you have a comment I hope to  
17 build on and not vitiate my comments.

18           DR. ELLISON: Those are excellent; I agree.  
19 I'd also like to see the EC50 independently of the  
20 mAbs, if they are a cocktail for instance I'd like  
21 to see if there's variation in the neutralizing  
22 capacity based on the strain. I think that would

1 be useful; also to ensure what epitope they bind to  
2 is linear conformational, make sure they're not  
3 overlapping. Those are the things I would consider  
4 or want to see off the top of my head.

5 DR. MOORE: I agree with both of those. The  
6 only thing I would add is I would like to see that  
7 when the in vitro test is done, that the challenge  
8 viruses are all equal in strength and that there  
9 should be evidence that that was determined before  
10 the testing.

11 DR. BADEN: We don't need to all be in  
12 agreement. It is okay for us to disagree. What I  
13 think is important is the rationale and thinking is  
14 shared so that the agency can hear the different  
15 lines of thought to be incorporated into their  
16 planning.

17 Dr. Burgess?

18 CAPT BURGESS: Just to follow on to the  
19 point, I completely agree that because of the  
20 importance, particularly for a U.S. indication,  
21 that diversity and antigenic diversity of  
22 particularly bad variants, not only that the virus

1 dose that's used in that in vitro assay be  
2 standardized, but also that there is reason to  
3 believe the flip side of that, that the cell type  
4 that the infection is occurring in is not  
5 artificially altering the perception of the potency  
6 of the antibody.

7 DR. BADEN: And the presumption of my  
8 comment, or an assumption in my comment, which is  
9 challengeable, is that one will have one product  
10 that's globally deployable rather than regionally  
11 deployable because of the practical implications.  
12 But that has an implicit assumption, where one  
13 could have an enhanced product for a geographically  
14 prevalent problem, but I just see the deployment  
15 and scalability, and approvability, and social  
16 usability too complex to make it viable. But that  
17 is a presumed assumption in the way I framed it.

18 CAPT BURGESS: But just a quick follow-on to  
19 that, I think the difficulty in regionalization is  
20 increasingly high, is exponentially high, when you  
21 get beyond in vitro neutralization or other  
22 antibody effector function activity. So the

1 emphasis should be on assessing potential regional  
2 variation, particularly in the in vitro infection  
3 neutralization assay.

4 DR. BADEN: And if I accept Dr Ellison's  
5 comments about the 4 cases in the last couple of  
6 years in the U.S., there is value in having a  
7 product that's active against variants in different  
8 species because of the cases that have occurred  
9 domestically. Therefore, the premium on making  
10 sure it's pan-protective and not a variant  
11 specific, because you really don't know.

12 Dr. Swaminathan?

13 DR. SWAMINATHAN: The rabies, I'll just  
14 address this, but I wonder if in addition to  
15 ensuring breadth of reactivity and potency of  
16 neutralization, once that has been optimized,  
17 whether concern needs to be paid to whether or not  
18 the epitopes are in more or less invariant regions  
19 of the genome, and whether that's practically  
20 feasible to optimize selection of monoclonal  
21 antibodies that are less likely to be escaped by  
22 mutation.

1 DR. BADEN: Dr. Ellison?

2 DR. ELLISON: That's important. I think  
3 that they should also demonstrate that if there  
4 isn't escape, the other antibody in the cocktail  
5 should be capable of neutralizing.

6 DR. BADEN: Well, are the escape variants  
7 well understood?

8 DR. ELLISON: No. They're artificially  
9 made.

10 DR. BADEN: Yes, so it becomes hard to know  
11 what the in vivo selection might be.

12 DR. ELLISON: No, you would produce the  
13 escape, and then you would ensure.

14 DR. BADEN: In vitro.

15 DR. ELLISON: In vitro.

16 DR. BADEN: Yes, but it's hard to know the  
17 applicability in vivo because of different  
18 selection system so to speak.

19 Other discussion on the in vitro challenges  
20 that should be thought about as part of a package  
21 to move forward?

22 Dr. Ellison?

1 DR. ELLISON: Who's going to be responsible  
2 for conducting the surveillance for this variance?  
3 The surveillance center at CDC, we only focus on  
4 plus and minus, rabid/not rabid. We typically  
5 don't go down to the molecular level unless there's  
6 a need to see that, investigate an outbreak, or  
7 something like that. And most of the phylogenetic  
8 studies that are done are not whole genome.  
9 They're based on actually a different gene  
10 altogether, nuclear protein, very highly conserved.

11 The glycoprotein is what we're talking about  
12 today, so who is responsible for conducting that  
13 type of surveillance?

14 DR. BADEN: I'm not sure we'll be able to  
15 answer that question and establish a new global  
16 system for monitoring rabies. However, I think  
17 what we can put forward is do we think that's an  
18 important piece of data to have? And if we think  
19 that's an important piece of data to have, then  
20 that can be something that we can suggest would be  
21 useful in a product development schema, so to  
22 speak. But your point's well taken as to who will

1 do it, under what aegis, under what quality, is not  
2 a straightforward matter. But do you think it  
3 would be important to know that, and how important?

4 DR. ELLISON: I think that would be  
5 incredibly important. We discover new lineages all  
6 the time. Also, taxonomically, there's only one  
7 species that's rabies. We've made these variants  
8 and strains ourselves. They're all arbitrary.  
9 Phylogenetically and taxonomically, it's just one  
10 virus, rabies. It has been compartmentalized into  
11 multiple hosts, and they do have independent  
12 signatures, but there's no formal naming structure  
13 for what we're calling variants, or strains, or  
14 isolates.

15 DR. BADEN: I think they're two different  
16 issues. One is to taxonomy. The other is the  
17 strain acquisition and sequencing so that data  
18 exist.

19 DR. ELLISON: I think that it's complex.

20 DR. BADEN: Dr. Ofotokun?

21 DR. OFOTOKUN: Mine is just a general  
22 comment, kind of agreeing with what has already

1       been said. I think, especially in this case, where  
2       the standard of care, what we have now is already  
3       very effective, I think the bar, whether in vitro,  
4       or clinical, or preclinical, the bar here should be  
5       really high. We need to ensure that whatever  
6       monoclonal antibody we have is broadly neutralizing  
7       against all the strains that are potentially  
8       available there.

9               So I think it will be important to see  
10       strong evidence of efficacy before this moves  
11       forward, and we will discuss that more as we move  
12       to the human data element with its ceiling  
13       challenge.

14              Dr. Weina, more on the in vitro discussion?

15              DR. WEINA: Yes, a really great intellectual  
16       question about monitoring for the strain variants  
17       and everything else, the question that pops into my  
18       head is so what? Really, I mean, how is that going  
19       to change what we do? We have a vaccine that  
20       hasn't changed. We have HRIG that we've been using  
21       that hasn't changed. We haven't changed the way  
22       that we produce the HRIG, and we haven't modified

1 it based upon the variance or possible shifts or  
2 escapes in it.

3 So the question is, while that  
4 intellectually is a really great question and may  
5 potentially come into play down the road, how does  
6 that really influence what we're doing in the  
7 development right now?

8 DR. BADEN: I think that's a terrific  
9 question. Do you think there's a difference  
10 between HRIG, polyclonal, and a monoclonal in terms  
11 of its potential activity against different  
12 strains, and is that relevant in the development  
13 path? Which you're arguing it may not be.

14 DR. WEINA: I'm arguing that it probably  
15 isn't where we're talking about taking at least  
16 2 monoclonals that are in overlapping regions. We  
17 still treat diseases that mutate like crazy with  
18 single drugs, and then wait until they just don't  
19 work anymore, and then come up with a new drug  
20 instead of doing what we do with HIV and treat with  
21 4 drugs. That's basically what they're doing with  
22 the monoclonal in India, is waiting until they have

1 something that escapes, and now they have to come  
2 up with another single monoclonal. We're just  
3 jumping ahead of the game there.

4 DR. BADEN: Dr. Burgess, did you have a  
5 comment on this?

6 CAPT BURGESS: I might take the opposite  
7 view that I think the bar is higher for a  
8 monoclonal cocktail that might just target 2  
9 epitopes, and that to me increases the importance  
10 of understanding the potential for epitope escape,  
11 compared to the standard of care, which is  
12 polyclonal and polyfunctional.

13 DR. WEINA: But that's assuming that the  
14 polyclonal, all of the different components of the  
15 polyclonal are important in the efficacy that we're  
16 observing. What if it's only a single monoclonal  
17 attacking a single glycoprotein that's actually  
18 doing anything? We don't know the answer to that,  
19 so it may only be one that's actually doing  
20 anything, and all the other garbage that we have in  
21 there is just carrier.

22 DR. BADEN: Dr. Swaminathan?

1 DR. SWAMINATHAN: Virologically, that's  
2 generally not true, that the serologic response to  
3 the capsid or the entire glycoprotein structure of  
4 the virus is extremely multifaceted in most cases.  
5 So the polyclonal response not only consists of  
6 multiple epitopes among one or more dominant  
7 proteins, but in fact includes multiple epitopes  
8 and multiple glycoproteins, depending on the  
9 complexity of the virus.

10 So I would think that it's highly unlikely  
11 that even though all of them may not be important,  
12 that they aren't multiple extremely redundant  
13 neutralizing capacities in HRIG. I think that's  
14 why it is potentially important because this has  
15 worked all the time without any problem being made  
16 the same way because it's essentially not one  
17 monoclonal; it's a whole boatload of monoclonals.  
18 It's a multiplicative function as to how likely it  
19 is that a given variant strain would escape  
20 2 monoclonals versus the number of reactivities in  
21 the polyclonal preparation. So I would be  
22 concerned about that issue.

1 DR. WEINA: No, I understand. But I think  
2 the point that I was trying to make is that I kept  
3 hearing probably and maybe. And we don't know for  
4 sure. When it comes to the immune system, we're  
5 like stone-age men looking at the inside of a  
6 computer and saying, "Hey, if I poke this, it'll  
7 spark." Unfortunately, that's true; that's my  
8 opinion.

9 DR. BADEN: I'm catching up to your imagery.  
10 (Laughter.)

11 DR. BADEN: Dr. Green?

12 DR. GREEN: I have a comment and a comment.  
13 The first comment is what we do know is the  
14 polyclonal is generated by giving the vaccines. So  
15 we know that our vaccine, which we think is  
16 effective, is generating multiple epitopes and not  
17 a single epitope. So this gives you pause about  
18 settling for one.

19 Maybe the solution is you either invest your  
20 money in saying we're going to make a cocktail that  
21 has more than 2 epitopes, even though the WHO  
22 decided 2 was adequate, and they have much more

1 expertise than I. I don't know the data nor  
2 understand the basis for that decision, but  
3 whatever the cost is to put 3 or 4 or 5 in, versus  
4 the cost to do the collection of virus that's out  
5 there to see if the mutant epitopes are prevalent  
6 or not, that's an economic question, because you  
7 could make a larger cocktail.

8           It just would cost more money to develop and  
9 it would probably cost more money to deliver versus  
10 collecting the specimens, which as soon as you're  
11 done collecting the specimens, you'd wonder if next  
12 week there was a new resistance mutation that  
13 emerged.

14           So I'm not sure of the answer, but in the  
15 end, I think that's an economic decision that  
16 you're looking at, and that could be decided -- if  
17 the economics are prohibitive on both sides, there  
18 may not be a sponsor interested in taking this up  
19 anyhow and that we don't even have an endpoint to  
20 all this conversation.

21           DR. BADEN: So I think we have clarity on  
22 the in vitro requirement. Any other suggestions on

1 the in vitro? Your point's well taken, and that is  
2 part of what will have to be weighed since we don't  
3 know. When you don't know, the risk is harm,  
4 versus you don't know and you're trying to move  
5 something forward. That's one of the challenges  
6 the agency is going to have to balance.

7 So if there aren't other comments on what  
8 would be beneficial in the in vitro package, then  
9 we'll move to the animal package, which I think  
10 Dr. Weina already provided a discussion about  
11 features to consider and how to look at the  
12 components individually and together. I think  
13 Dr. Green has more discussion on that.

14 DR. GREEN: This is to add to what Dr. Weina  
15 said, is what you're looking at. We keep saying  
16 human RIG, human RIG, human RIG, but as I  
17 understood it, parts of the world that we would be  
18 doing our clinical trials might be using equine  
19 RIG, which then suggests that when we're doing the  
20 in vivo studies, we should include a set of  
21 experiments that also look at equine RIG because  
22 that's the comparative that's likely going to be in

1 place.

2 DR. BADEN: Dr. Burgess?

3 CAPT BURGESS: If we could just transcend  
4 the junction that we just made on the animal side  
5 to ask the question again -- and this would be a  
6 question of rabies experts -- would you consider an  
7 antibody that didn't appear to have neutralizing  
8 activity in the available neutralization assay but  
9 which had binding activity, and then demonstrated  
10 protection in an animal model if a sponsor chose to  
11 do that? Which is a different existential  
12 question. In other words, would lack of  
13 neutralization activity in what's articulated here  
14 as step 1, be a dead end?

15 DR. BADEN: So gatekeeper.

16 CAPT BURGESS: Because I would say no, but  
17 I'm not a rabies expert.

18 DR. BADEN: Dr. Moore or Dr. Ellison, would  
19 you wish to engage?

20 DR. MOORE: I would say from the  
21 publications that I know that have looked at  
22 monoclonals that are comparing monoclonals that are

1 neutralizing compared to monoclonals that are just  
2 finding, that you definitely need to have the  
3 neutralizing component; otherwise you're not going  
4 to stop the virus. I haven't known of any animal  
5 studies that have done that just in vitro.

6 DR. BADEN: So to amplify Dr. Burgess' point  
7 just for the record, the question is, is  
8 neutralization really the proper gatekeeper since  
9 we don't understand protection? And may developers  
10 want to think about that as they develop their in  
11 vitro package? Where if they have other reasons to  
12 believe that a non-neutralizing antibody may work,  
13 they can make that argument, and then it would have  
14 to make sense based on the available data. But at  
15 this point in time, neutralization is the light  
16 post, pending information that can be directive.

17 Dr. Siberry?

18 DR. SIBERRY: In terms of the animal  
19 challenge studies, I just want to confirm that  
20 we're recommending that there be both a challenge  
21 that's immunoglobulin alone, the monoclonal against  
22 poly, and then immunoglobulin with vaccine, because

1 I think part of this is understanding how it would  
2 be given in humans if it got that far and also the  
3 potential for interference.

4 So am I understanding correctly that we  
5 think both of those sets should happen with and  
6 without vaccine?

7 DR. BADEN: I don't think it's we. Each of  
8 us should be putting forward things that we think  
9 are relevant to be considered in the preclinical  
10 package. And if I hear you correctly, that the  
11 proper studies preclinically in the animal model  
12 should include the novel product, and as previously  
13 mentioned, may even do it individually, as well as  
14 in a cocktail, and with or without the vaccine  
15 adjuvant, so that one understands how that behaves.

16 I would build on that in the sense of -- and  
17 I know that the ability to do human studies are  
18 here, but one could imagine the Animal Rule not  
19 applying to this, but there are parameters  
20 associated with the Animal Rule that could fortify  
21 the data presentation, where one could imagine to  
22 animal challenge models done in a way that could

1 show efficacy as supportive data to the overall  
2 packet that demonstrates.

3 That I would defer to our experts as to  
4 which animal model recapitulates the disease well  
5 enough to be able to demonstrate efficacy; and  
6 that's, in addition to defining the elements, it's  
7 doing the studies that show the final product  
8 behaves in a way that would be reassuring. I think  
9 that might also strengthen a packet that would  
10 provide evidence, given what we can do in  
11 well-controlled circumstances, because I think  
12 Dr. Follmann's many points about you don't actually  
13 know if they were exposed is going to be a  
14 fundamental challenge in any human exercise of  
15 studying this.

16 Dr. Brown?

17 DR. BROWN: I'm sorry. I'm a little bit  
18 slow. I wanted to go back to the comment around if  
19 we were looking at a mAb that demonstrated binding  
20 but not neutralizing, I actually think that that  
21 would have consequences for the rest of what has  
22 been proposed for how we would -- like the

1 serologic endpoint conversation and everything. So  
2 I actually think that's a bigger issue and might  
3 make it a no-go, at least for this proposed  
4 pathway.

5 DR. BADEN: I'm not sure I -- so if we were  
6 to consider binding alone, then the rest of the  
7 discussion we're having is undermined?

8 DR. BROWN: Yes, because we're relying so  
9 heavily on neutralizing antibody measurements for  
10 some of our endpoints.

11 DR. BADEN: To work with your point, let's  
12 say that there was some other assay developed that  
13 we haven't thought about today, but three years  
14 from now, technology advances, and there's a better  
15 way to measure an immunologic parameter that we  
16 think is much more tightly correlated with  
17 protection. Couldn't that then just replace the  
18 discussion for the mAb?

19 DR. BROWN: Yes, absolutely, but I've been  
20 working in rabies a long time, and I'm not a  
21 virologist, but this has not changed. This is what  
22 we know about how to measure surrogates of

1 protection. I'm having a hard time imagining  
2 something that's going to show up in the next three  
3 years. However, theoretically, yes, you are  
4 correct.

5 DR. BADEN: Because to minimize vitiating  
6 our whole discussion, I think that if we look at  
7 the in vitro element as what are the  
8 state-of-the-art data that establishes the in vitro  
9 activity? Currently, it's the mAb discussion; our  
10 discussion is based on that.

11 If something were to emerge that takes its  
12 place, my hope is the field would use the latest  
13 science to guide the discussion, but that would  
14 then alter how one assesses the surrogate or  
15 correlate, and I would hope that we would be open  
16 to the latest innovation based upon what technology  
17 can do.

18 For the purposes of our conversation, we're  
19 going to call that the neutralizing antibody  
20 because that's the current state of the art, but I  
21 accept the point that that state of the art should  
22 be fluid with the state of the art at the time the

1 discussion occurs; so point well taken.

2 Back to the animal discussion. I think  
3 Dr. Burgess, didn't you have a comment?

4 CAPT BURGESS: It was just a follow-up on  
5 two relevant models that recapitulated disease, but  
6 the comment I think we heard that that may limit  
7 the strains that could be assessed.

8 DR. HARRIST: Just to follow that up, I do  
9 think, if it's at all possible, to think about use  
10 in the United States, those bat strains that we  
11 know are most common here. I would like to see  
12 that if at all possible.

13 DR. BADEN: Other comments on the animal  
14 model element? Dr. Follmann?

15 DR. FOLLMANN: Yes, a couple comments.  
16 There was discussion earlier on the animal model  
17 about it would be nice to look at diversity of  
18 challenge viruses I guess. If you're going to do  
19 that, and there's utility in doing that, you might  
20 want to have a placebo group, an HRIG group, as  
21 well as a monoclonal antibody group. I don't know  
22 if you were thinking just using monoclonal antibody

1 versus placebo would be efficiency; you'd need  
2 3 arms.

3 Then just to follow up on a comment  
4 Dr. Siberry made, where I think he said you'd want  
5 to study this without vaccine, basically, the  
6 monoclonal without vaccine. And that could lead to  
7 I guess useful information, but if it fails there,  
8 how bad is it if it's always going to be given with  
9 vaccine?

10 If we were looking at a vaccine that had  
11 peptide and adjuvant, we wouldn't care about how  
12 the adjuvant alone or the peptide alone worked. So  
13 if it's going to always be given in combination,  
14 that's the relevant thing. And if you're going to  
15 do that, just monoclonal antibody alone, you'd  
16 probably want to do HRIG alone as well to see.  
17 Maybe it would fail also.

18 DR. SWAMINATHAN: So I think you clearly  
19 have to do it with vaccine. I thought I had heard  
20 a proposal that you also do it without vaccine.  
21 And maybe I misheard.

22 DR. WEINA: No. I think it's important that

1     you do it without the vaccine. I think it's  
2     critically important to tease out how much are we  
3     actually getting, protection-wise, without the  
4     vaccine being present at all. Without wound  
5     cleansing being present, without vaccine being  
6     present, how much protection are we actually  
7     getting from the equine or human?

8             I think that was a great point to try both,  
9     and this would ideally, I guess, be 4 arms:  
10    placebo, 1; equine, 1; human, 1; and the  
11    monoclonal, but without the vaccine. I think that  
12    that's critically important to do it without the  
13    vaccine.

14    But that really needs to be teased out.

15             DR. BADEN: Dr. Swaminathan?

16             DR. SWAMINATHAN: Maybe I misheard before,  
17    but I heard it at least in one of the animal models  
18    that a vaccine actually doesn't do much, or  
19    anything. So I think we have to be cognizant of  
20    the limitations of the implications. You have to  
21    compare something where HRIG actually works, and  
22    that's sort of the crux of it, to me.

1 DR. BADEN: The issues of the model, and the  
2 strain, and the clinical phenotype are all  
3 persnickety. So making sure that the intervention  
4 gives the result you're interested in, given the  
5 limitations and challenges of the model.

6 DR. SWAMINATHAN: And that was part of the  
7 problem with  
8 thinking about just actually having one animal  
9 model because we know from doing drug trials that  
10 even when you have 2 animal models and they show  
11 absolutely nothing, you put it into a human and all  
12 hell breaks loose. So you're always doing that.

13 DR. BADEN: Dr. Follmann, did you have a  
14 follow on or not?

15 DR. FOLLMANN: No.

16 DR. BADEN: Any other  
17 follow-on -- Dr. Green? Sorry.

18 DR. GREEN: I just want to support the  
19 notion of doing it with and without. I think it  
20 does give you some sense of biologic activity, and  
21 if the vaccine didn't work at all, then you  
22 wouldn't need to do it, but you wouldn't need to

1 give the vaccine. This gives you just some sense.

2           It also may give some -- if you're really  
3 going to do this completely, you also, as I think  
4 was discussed, are going to do your intervention at  
5 delayed times and early imprompt times. So you  
6 expose 6 hours, 12 hours, 3 days, 7 days with and  
7 without vaccine. And you could almost imagine that  
8 the more effective the antibody is, the more  
9 important it is if you have delay. Because you're  
10 going to always have that built-in delay for the  
11 vaccine to go, and when you cross a certain  
12 threshold -- and we've heard earlier that once the  
13 virus hits the central nervous system, it doesn't  
14 matter what you do. So getting that sense of  
15 single potency gives me some sense of -- I'd like  
16 to know that.

17           If you had a family that had been bitten and  
18 came in belatedly for whatever reason, you would  
19 feel better to know that you had some sense that  
20 this thing has activity on its own because you're  
21 not going to get anything from the vaccine for a  
22 couple of weeks anyhow.

1 DR. BADEN: I think, in part, the animal  
2 model is so important because it's a highly  
3 controlled known infection, even though the model  
4 is extremely difficult. And once we go into  
5 people, we have no idea if there was an exposure.  
6 We have ways of trying to assess the risk, but  
7 ultimately, other than the 20 cases where they  
8 bring in the animal's head that can be dissected,  
9 it's extremely unusual to have confirmation.

10 Dr. Follmann?

11 DR. FOLLMANN: Just a brief comment on  
12 Dr. Green's comment, I think a better way to study  
13 that, the concern about variable times coming in,  
14 would be to give vaccine and antibody variable  
15 times after exposure in the animal model. Because  
16 generally they'd be getting antibody and vaccine,  
17 so you'd like to know how efficacious it is after  
18 1, 2, 3, 4, 5, 8 days delay from exposure in the  
19 animal model.

20 DR. GREEN: I'm not disagreeing with that.  
21 I'm saying I want to see both aspects of it, again.  
22 I just think of it as someone who treats patients,

1 to have a sense of what it does on its own gives  
2 you some sense of potency, really. So if it turned  
3 out that you got some efficacy from polyclonal  
4 alone that you weren't getting from the cocktail of  
5 monoclonal, I would just give pause, particularly  
6 for approval in the United States, which means it  
7 might become the alternative approach, that you  
8 might be using a product that's a little bit less  
9 efficacious, a little bit inferior, you don't know,  
10 and you'd be offering it as an alternative to  
11 something that's available and efficacious.

12 I get in a shortage scenario, it would be  
13 great to have that backup. But if it was your  
14 little child that was asleep and woke up with a  
15 bat, and particularly if they tested the bat and it  
16 was positive, you would just want the maximum that  
17 you could give because if you fail, you know, it's  
18 fatal.

19 DR. BADEN: If no further discussion on  
20 aspects of the animal model to consider, then we  
21 can open discussion on the phase 1 human data,  
22 non-rabies exposed. What kind of well-controlled

1 human data of safety, efficacy, however we define  
2 it in a sort of that phase 1 model?

3 FEMALE COMM MEMBER: Can you bring up the  
4 slide with numbers? [Inaudible - off mic].

5 DR. BADEN: But is that numbers for the  
6 phase 1 or is that numbers post-exposure?

7 FEMALE COMM MEMBER: [Inaudible - off mic].

8 DR. BADEN: I thought the numbers had more  
9 to do with the sensitivity of detection in the  
10 exposed. I'm dividing it between healthy volunteer  
11 studies, where you understand the kinetics of the  
12 Ig and the vaccine response and any interference,  
13 which can be highly controlled; and then what to do  
14 in the field where there may or may not be  
15 exposures because my dog bit me, or more, your dog  
16 bit me, and you won't give me the dog.

17 Dr. Siberry?

18 DR. SIBERRY: Just to start off, because we  
19 had some discussion about children, to say that I  
20 think we should make sure that men and women are  
21 represented in these since there could be sex  
22 differences; probably not, but important; but that

1 children and pregnant women would only come in  
2 likely in the rabies-exposed studies when we  
3 discuss them later.

4 DR. BADEN: Dr. Green?

5 DR. GREEN: Just men and women and also  
6 looking at the range of adult ages. So you want to  
7 look at this at people that are in their 20's, and  
8 then people that are in there, whatever, 50's, and  
9 their 70's, or whatever you can get in terms of  
10 volunteers. But we know that we handle things  
11 differently at different ages.

12 DR. BADEN: Dr. Follmann?

13 DR. FOLLMANN: Just that these studies  
14 should be done in the U.S. and overseas, where we'd  
15 be doing the field trials.

16 DR. BADEN: I think even though we've been  
17 reassured that the vaccine response is so powerful  
18 that it will overcome the Ig given, I think we need  
19 to understand what interference or have the data to  
20 reassure ourselves there is no interference, and  
21 how much tolerance we have in the variability of  
22 the dose and potency of the monoclonal to make sure

1 it doesn't then interfere with the vaccine take. I  
2 think that's easily done and that needs to be done  
3 in light of the different vaccines that it might be  
4 paired with, at least major vaccines that it's  
5 likely to be paired with.

6 Dr. Swaminathan?

7 DR. SWAMINATHAN: I just wanted to second  
8 what Dr. Green said about the age. We just know  
9 from various vaccines how variable the age-related  
10 response can be. Also, with respect to what you  
11 said, the interference may be much greater in  
12 somebody who is not responding optimally to the  
13 vaccine.

14 DR. BADEN: And whether or not there are any  
15 genetic backgrounds that may impact response. It  
16 was pointed out that the failure with the HRIG in  
17 the Iranian study, there wasn't evidence of a  
18 vaccine response. You can't say there wasn't, but  
19 there wasn't evidence of one, and perhaps there are  
20 other genetic backgrounds, or age, or other factors  
21 that may influence; so  
22 at least understanding that the response in a

1 general sense transcends any given genetic  
2 background.

3 Other thoughts on the -- Dr. Follmann?

4 DR. FOLLMANN: In Appendix C, there was a  
5 discussion about how would we define interference  
6 if the antibody was above 0.5, I guess,  
7 international units per milliliter at 14 days or  
8 so, and they suggested three different ways you  
9 could do that. The way that made most sense to me  
10 was to just pick a later time point when the  
11 antibody would presumably be cleared even if it's  
12 substantial at day 14, and then look at that.

13 DR. BADEN: So I guess the question that  
14 you're getting at, is it day 7 peak that matters  
15 versus day 14, or 28, or a later time point?

16 DR. FOLLMANN: I wasn't getting so much of  
17 that. I think I just wanted to say we want the  
18 vaccine to have durable protection. We want it to  
19 be above that 0.5, and to me the simplest way to do  
20 that would be to measure are you above 0.5 at  
21 day 28, 56, and so on.

22 DR. BADEN: But do we want durable? I guess

1 I'm not -- is this about durable protection or is  
2 this about blocking that initial exposure? Just  
3 thinking about the target profile of this, is it  
4 that I'm protected for rabies for the rest of my  
5 life or the bite last week isn't going to do me in?

6 DR. FOLLMANN: Well, I think they felt that  
7 the correlate of protection is 0.5 international  
8 units, so you want to continue to have an antibody  
9 above that for a long period of time. So whether  
10 it blunts it by a log or two or three, maybe that's  
11 bad, but as long as it continues to bump 0.5 for a  
12 long period of time, you should still be okay.

13 Anyway, I was answering a more narrow  
14 question, which was what do you do about measuring  
15 interference if there's a lot of monoclonal  
16 antibody at day 14, three different ways to try and  
17 address that issue? And they made three  
18 suggestions. I prefer the one that says look at  
19 day 28 or 56 to be above 0.5.

20 DR. WEINA: And toward that point, one of  
21 the things that I thought of as I was reading  
22 through the Appendix C was the fact that however

1 long you decide to follow it, you're going to have  
2 a lot of lost to follow-up potentially in this  
3 population.

4 So the trial would have to purposefully be  
5 looked at so that you didn't have the same  
6 requirement of numbers that have their neutralizing  
7 antibody measured a year out as they did 14 days  
8 out, just so that you didn't lose too many people  
9 at follow-up because I've seen that in clinical  
10 trials, where they have these extremely long  
11 follow-ups, and then we're missing the main point  
12 because we're trying to do everything.

13 DR. BELL: I guess you'd have that luxury in  
14 the healthy volunteer versus the exposed patients.

15 DR. WEINA: But even in healthy volunteers,  
16 you might lose some.

17 DR. BADEN: But in the healthy volunteers,  
18 should this be placebo controlled? Should this be  
19 active-comparator controlled? These are not exposed  
20 individuals. What's the right way to make the  
21 assessments that we want them to make?

22 DR. GREEN: Two comments. First to what you

1 just asked, I think because you're looking at  
2 interference, then you do want controls that get  
3 vaccine without exposure to the antibody and get  
4 vaccine with exposure to the antibody, and then  
5 you're going to need various potential vaccines.  
6 And you probably have to do the various potential  
7 antibodies, so that's HRIG, ERIG, and the cocktail.

8           Then just to the timing of levels, if  
9 money's no object and subjects will agree to -- or  
10 participants, excuse me, that's the correct term  
11 here -- and participants would agree to it, it  
12 seems to me you would want early and a little bit  
13 later because you're interested in the kinetics of  
14 getting vaccine-associated protection. So if you  
15 blunt it totally or just delay it, you'd want to  
16 know both of those pieces of information relative  
17 to what we do now.

18           So again, the limitations of this is how  
19 much money you're willing to spend and how willing  
20 your participants are to come in and be seen and be  
21 stuck on separate occasions. But in an ideal  
22 world, when you're drawing it up, I would do all

1 those variations and early and later blood draw.

2 DR. BADEN: But part of this is what's the  
3 critical path of information that would reassure us  
4 that the product being developed makes sense?  
5 There will always be 101 more permutations, and I  
6 think that's part of how --

7 DR. GREEN: But again, if we think that the  
8 real protection is coming from vaccine and that the  
9 purpose of the antibody is to cover you until the  
10 vaccine gets in, it seems it would be important to  
11 know whether or not -- maybe we already do know  
12 this. It would be important to know whether or not  
13 the new cocktail does anything in terms of timing  
14 to getting to the critical point, and to your point  
15 earlier, perhaps more importantly is whether you  
16 have protection still at a month, and certainly at  
17 6 months or a year. I think that's a different  
18 question and a different purpose of the vaccine.

19 DR. BADEN: Dr. Burgess?

20 CAPT BURGESS: I don't know if this is  
21 critical path or the 102nd, 115th permutation, but  
22 definitely route of administration of vaccine,

1 given ex-U.S. versus U.S. But then the question of  
2 not only different vaccines, but as was raised in  
3 the background and the extant question about  
4 different vaccines given in the same post-exposure  
5 series, whether or not it is important to have  
6 phase 1 data about vaccine interference in that  
7 context. I don't know. That question was asked,  
8 but I don't know.

9 DR. BADEN: We shall move to the exposed,  
10 the phase 2B -- I'm sorry. Dr. Troy?

11 DR. TROY: That applies to the third  
12 question. So do we want to wait for that until  
13 after the voting.

14 DR. BADEN: Thank you. I appreciate  
15 guidance.

16 So we have about 10 minutes until a break,  
17 so we can do the vote on the preclinical early  
18 clinical package, so this is question 2, voting.  
19 I'll read the question, and then we can vote yes or  
20 no or abstain.

21 Would clinical trials of an investigational  
22 mAb cocktail product as part of post-exposure

1 prophylaxis in rabies virus-exposed subjects be  
2 acceptable if the data package available to support  
3 trial initiation included the following elements:  
4 cell culture data demonstrating breadth of  
5 coverage -- we've had that discussion -- animal  
6 challenge studies demonstrating survival benefit;  
7 and clinical studies in healthy volunteers, not  
8 rabies virus exposed, demonstrating a similar  
9 half-life, comparable early RVNA levels, and  
10 comparable vaccine interference of the mAb cocktail  
11 versus human rabies immune globulin? If no, what  
12 additional data elements would be needed?

13           So we'll pose the question. If these data,  
14 as we've been discussing, were available, would  
15 this be a foundation that would allow a trial to go  
16 forward in exposed individuals? After we vote,  
17 then we can highlight any elements that have not  
18 already been highlighted.

19           The voting has been initiated and your light  
20 should be blinking. It will keep blinking, and you  
21 can press it as many times until the blinking  
22 stops, and that's where your votes stands.

1 (Voting.)

2 DR. BADEN: The voting results are 16, yes;  
3 zero, no; zero, abstaining; zero, no voting.

4 So what I would open now -- and when we can  
5 start on the right side of the room with Dr. Brown.  
6 You don't need to reiterate what we've already  
7 said. If there's anything that we haven't  
8 discussed -- and this would have been more  
9 important if someone had voted no as to what would  
10 be missing. But if there's anything that has not  
11 been discussed that should be highlighted, we'll go  
12 around the room and everyone can highlight that,  
13 and then we'll have the break before we go to part  
14 2, which is the more challenging element.

15 Dr. Brown?

16 DR. BROWN: I don't have anything to add.

17 DR. BADEN: Dr. Moore?

18 DR. MOORE: I don't have anything either.

19 DR. BADEN: Dr. Ellison?

20 DR. ELLISON: Nothing to add.

21 DR. BADEN: Dr. Harrist?

22 DR. HARRIST: Nothing.

1 DR. BADEN: Dr. Baker?

2 DR. BAKER: No additions.

3 DR. BADEN: Dr. Porter?

4 DR. PORTER: Nothing to add.

5 DR. BADEN: Dr. Burgess?

6 CAPT BURGESS: Nothing to add.

7 DR. BADEN: Procedurally, we don't need to  
8 confirm our vote. Okay. I need to stay on the  
9 right side of the rules.

10 Dr. Burgess?

11 CAPT BURGESS: Nothing to add. I voted yes.

12 DR. BADEN: Okay. We'll have to start again  
13 with Dr. Brown.

14 (Laughter.)

15 DR. BADEN: Just say what your vote was.

16 DR. BROWN: I voted yes.

17 DR. BADEN: Dr. Moore?

18 DR. MOORE: I voted yes.

19 DR. BADEN: Dr. Ellison?

20 DR. ELLISON: Yes.

21 DR. BADEN: Dr. Harrist?

22 DR. HARRIST: I voted yes.

1 DR. BADEN: Dr. Baker?

2 DR. BAKER: Yes vote.

3 DR. BADEN: Dr. Porter?

4 DR. PORTER: Yes.

5 DR. BADEN: Dr. Burgess, I'll skip. You  
6 already voted yes.

7 DR. BADEN: Dr. Ofotokun, what your vote was  
8 and if anything to add.

9 DR. OFOTOKUN: I voted yes, and I have no  
10 additional comment.

11 DR. BADEN: Dr. Follmann?

12 DR. FOLLMANN: Yes, nothing to add.

13 DR. BADEN: Dr. Clark?

14 DR. CLARK: Yes, nothing to add.

15 DR. BADEN: Yes, nothing to add.

16 Dr. Weina?

17 DR. WEINA: Ditto. Yes, nothing to add.  
18 Sorry.

19 DR. BADEN: Please vote yes so I don't have  
20 to re-vote.

21 Dr. Green?

22 DR. GREEN: Yes, nothing to add.

1 DR. BADEN: Dr. Gripshover?

2 DR. GRIPSHOVER: Yes, nothing to add.

3 DR. BADEN: Dr. Siberry?

4 DR. SIBERRY: Yes, nothing to add.

5 DR. BADEN: Dr. Swaminathan?

6 DR. SWAMINATHAN: Yes, nothing to add.

7 DR. BADEN: So it is now 2:54. We will take  
8 our break.

9 Can we resume at 3:10? And we will take up  
10 the second half of the discussion. We're now on  
11 break.

12 (Whereupon, at 2:54 p.m., a recess was  
13 taken.)

14 DR. BADEN: Time to take your seats. We  
15 shall resume the second part of the discussion and  
16 voting elements. I would like to thank Dr. Troy  
17 again for keeping me on target.

18 (Laughter.)

19 DR. BADEN: The way we will proceed is  
20 element number 3 in our handout, or question  
21 number 2, or discussion item number 2, which is  
22 associated with question number 2. We will discuss

1 the issues that we think are relevant for a  
2 biologic license application, a BLA, and that will  
3 get into the elements of what types of studies in  
4 exposed individuals and what kind of safety are  
5 needed. We will then vote on whether or not we  
6 think the path proposed is a reasonable one for  
7 potential licensure consideration.

8 After we have that vote, you can put up the  
9 question or the discussion element. After that, we  
10 will then have any postmarketing discussion. So  
11 the discussion and question will be around the  
12 elements appropriate for a BLA application;  
13 afterwards, what additional information will be  
14 valuable in a postmarketing setting. So we'll try  
15 to separate those two elements.

16 Discussion item 3, which is really  
17 discussion item 2 for question number 2, this  
18 discussion item is information needed to support  
19 submission of a biologic license application, BLA.  
20 In addition to what we've already discussed, cell  
21 culture, animal challenge, healthy volunteer  
22 clinical data, please discuss the type and amount

1 of clinical data in rabies-exposed individuals  
2 needed to support submission of a U.S. BLA for a  
3 rabies mAb cocktail as part of post-exposure  
4 prophylaxis or PEP.

5 I'd like to open the floor to discussion of  
6 the elements that would be valuable for to support  
7 a BLA for approval. Dr. Green?

8 DR. GREEN: Dr. Baden, I was wondering if  
9 you want to direct this as you did with question 1,  
10 since there's an A, B, and C to this approach as  
11 well.

12 DR. BADEN: I wasn't planning to --

13 (Laughter.)

14 DR. BADEN: -- in that I think that this  
15 element will require a discussion of all of these  
16 factors, and I'm happy for you to discuss A, to  
17 start discussion on A, but I think they're going to  
18 be heavily intermixed because I think the issue of  
19 a thousand participants with the mAb and the lack  
20 of mortality in 750 may have some overlap as to who  
21 those individuals are.

22 But we'll open the floor to discussion, and

1 I think that some of the power discussion, some of  
2 the assumptions of a 99.5 percent versus a 99.9  
3 percent, the tables that you had previously  
4 referenced, Dr. Green, related to what level of  
5 power do we think is acceptable to be able to move  
6 forward, realizing there will always the potential  
7 for more data to have greater precision, and what  
8 level of precision is adequate to move forward  
9 given the potential utility of having more products  
10 in this space.

11 Any takers to start the discussion?

12 Dr. Kartsonis?

13 DR. KARTSONIS: I just would make one  
14 comment as it pertained to the lack of mortality in  
15 greater than 750 subjects, which I think makes a  
16 lot of --

17 DR. BADEN: Speak closer to the microphone,  
18 please.

19 DR. KARTSONIS: Oh, sorry. I just wanted to  
20 make a comment about the lack of mortality in  
21 greater than 750 subjects. I would ask that we  
22 also consider, if we are going to also have an

1 active control group in there, whether or  
2 not -- that it would be also -- my worry is you may  
3 end up having 1 in 2, or 2 in 2, depending on the  
4 type of cases you get. My worry is about a very  
5 strong lack of no mortality in 750 may need to be  
6 balanced relative to what you also see in the  
7 comparator group. That was the only thought I had  
8 in terms of that.

9 DR. BADEN: Point well taken, but to expound  
10 on the principal, I think the principal is if  
11 there's a comparator, then one can have some  
12 assessment if the misbehavior is disproportionate,  
13 although it's very hard in this setting to assess  
14 that because the anticipation is 0 and 0 or it may  
15 be 1 and 0, and just random between the two groups,  
16 depending on the environment, the exposure.

17 But how do we feel about the 99.5, putting  
18 forward that 99.5 is adequate to move forward in  
19 this ceiling effect situation and opacity as to the  
20 nature of the exposure? So we're not really clear  
21 on the ceiling effect. Dr. Harrist?

22 DR. HARRIST: Thank you. Well, I think it's

1       been said before, too, but I would agree that as  
2       somebody who would be recommending post-exposure  
3       prophylaxis to somebody, and knowing that we had  
4       something that's 99.9 percent effective, again,  
5       that's sort of a guesstimate, too, but it's the  
6       best information we have, versus something that's  
7       99.5 percent, and that hasn't likely been studied  
8       in the United States very extensively, it would be  
9       hard for me to either recommend equally or to  
10      recommend the monoclonal antibodies with the 99.5  
11      percent.

12               Now, in a situation where there wasn't HRIG  
13      available, then, yes, I think it'd be great to  
14      have, but it's hard to picture a scenario in which  
15      I could --

16               DR. BADEN: So are you arguing or -- I don't  
17      mean to be argumentative, but are you sharing a  
18      perspective in the sense that adequacy for approval  
19      or adequacy to recommend?

20               DR. HARRIST: Adequacy to recommend.

21               DR. BADEN: But could you imagine approval  
22      at let's say 99.5, realizing that practitioners

1 would have to be aware of that, and that might  
2 influence selection of agent, at least locally?

3 DR. HARRIST: Yes, I think that's fair.

4 DR. BADEN: Dr. Weina?

5 DR. WEINA: I just wanted to comment that  
6 the idea of lack of mortality in greater than 750  
7 subjects is -- in an ideal world, yes, it would be  
8 really great to have that. But trying to look at  
9 it from a practical standpoint, the Indian trial,  
10 2 years to do 200 people, given the issues of  
11 recommendation, we've got something that's 99.9  
12 percent effective already, are you going to take a  
13 chance that you're that one bad guy in the group  
14 that's 99.5 percent? Are you really going to  
15 enroll in that trial or not?

16 Then there was variability -- the point I  
17 want to get to is that we have to be practical in  
18 the standpoint that you can't restrict the  
19 enrollment to only people that are going to get  
20 there within 24 hours and get everything ideally  
21 placed and everything else. But if you're going to  
22 say, hey, we need 750 people to reach this area,

1 reach this limit, we have to be really careful that  
2 everybody is assessed at the time that they get it  
3 for the adequacy of how it was administered, when  
4 they came in, and everything else, and try and  
5 enroll as many as you can, but get as much data as  
6 you can on every single one, so that you can do an  
7 adequate post-mortem if you have to or if they  
8 don't make it, and see if it's reasonable that they  
9 died; otherwise you're just never going to get the  
10 numbers. You aren't going to get a sponsor that's  
11 going to do a 20-year study to enroll 750 people.

12 DR. BADEN: So are you suggesting that there  
13 should be a phase-in of the nature of the exposure,  
14 where the non legs first, there's some evidence  
15 that it doesn't fail, and then you move to a higher  
16 risk, or do you think you should just go right to  
17 higher risk?

18 DR. WEINA: No. I think the initial one  
19 that they're talking about, that they had suggested  
20 in which you take lower risk individuals first and  
21 then go to the higher risk individuals is fine.  
22 But I still think that you have to try and make

1       sure that in our search for as much perfection as  
2       we can, so that there's not a lot of Monday morning  
3       quarterbacking when everybody really wants the  
4       vaccine, but they don't want any risk associated  
5       with it, it's just not realistic.

6               So at some point, you have to balance the  
7       practicality with the idealism that you're going to  
8       get a perfect vaccine, which you're never going to  
9       get.

10              DR. BADEN:  Dr. Swaminathan, did you have a  
11       follow --

12              DR. SWAMINATHAN:  The concern I have about  
13       recommending something that one can't say for  
14       certain is noninferior is real, but as I think you  
15       pointed out, it needs to be divorced from whether  
16       we're talking about valid -- rationalizing a  
17       license application or making a clinical decision  
18       on the use of that agent.

19              There are many drugs that are in guidelines  
20       as second-line use when the first drug can't be  
21       used, isn't available, or in a mass casualty  
22       setting, for example.  And without the existence of

1 those alternative agents in some of those  
2 extenuating circumstances, it would be extremely  
3 difficult and could lead to mass morbidity and  
4 mortality.

5 So I think there are public health reasons  
6 to support an application that may not completely  
7 overlap with individual clinical decisions.

8 DR. BADEN: Dr. Follmann?

9 DR. FOLLMANN: When I came here, I was  
10 thinking of this more as 750 gives you -- if you  
11 have zero mortality, you can have 99.5 percent  
12 survival rate or better, and then we'd go on to the  
13 6,000-person study. This is the way I was thinking  
14 of the FDA's proposal, and then presumably we'd  
15 rule out 99.9, and just thinking one would follow  
16 after the other, not thinking through the issue  
17 that if it's licensed, it would be available after  
18 the 750 and could be used widely.

19 But then, in reading the question, I noticed  
20 that there were two possibilities. One would be  
21 after the 750, it would be available to everyone,  
22 or after the 750, it would be recommended as the

1 second-line therapy. I'd much prefer that sort of  
2 licensure or approach because I really want the  
3 6,000, and I fear if -- if it's recommended a  
4 second line, there's a much greater chance of  
5 getting the 6,000.

6 So I'm thinking of how would I want to  
7 approach this as being available, I'd want the  
8 6,000 ultimately. So I think second line after the  
9 750 would be the preferred a labeling.

10 DR. BADEN: I guess I want the 250,000 after  
11 KEDRAB, but it's how do you get there. It's how do  
12 you have the initial data that says it's reasonable  
13 to keep going forward --

14 DR. FOLLMANN: Right.

15 DR. BADEN: -- and that initial data will be  
16 collected in a high-resolution settings, so you  
17 have greater certainty in the measurements, because  
18 as you get bigger and bigger, you may not be able  
19 to measure a car accident. It just becomes harder  
20 as you get larger numbers to have the same high-  
21 resolution follow-up.

22 So to some degree, as you are suggesting,

1 for the BLA, what in the postmarketing, and then  
2 what in the post-postmarketing as one looks at  
3 different formats of scale-up in different  
4 environments. I'm still struck by 17 million  
5 treated, 60,000 deaths annually, that there is a  
6 current global unmet need that the current  
7 available products aren't meeting for whatever  
8 reason. I'm not passing judgment as to why we have  
9 59,000 deaths globally, but that is going on, and  
10 how to have more tools to help address that, and  
11 then would need to collect all the data you're  
12 suggesting.

13 DR. FOLLMANN: Right. So the scenario I  
14 don't like is it's approved after 750, you don't  
15 get the 6,000, and we don't know. I want to avoid  
16 that.

17 DR. BADEN: Fair enough. Dr. Ofotokun?

18 DR. OFOTOKUN: I don't even know how we get  
19 750 participants to do this type of study, for two  
20 reasons. The outcome we're looking at here, it's  
21 fatal. If your product, if it doesn't -- it's not  
22 as good as the standard of care. The risk involved

1 is very high. And the standard of care, as we've  
2 seen already, if we do everything right, it's over  
3 99 percent.

4 I find that if you take this to the field,  
5 how do you even tell participants I have a product  
6 that is 99 percent effective? I have another  
7 product. I'm not sure; it could be quite as  
8 effective. How do you even sell that? I wouldn't  
9 in good conscience as a clinician, in a clinical  
10 trial, offer that to my participant. So I still  
11 see a lot of -- I struggle with how do we even get  
12 to 750.

13 DR. BADEN: And you struggle because of how  
14 do you portray it to the volunteers --

15 DR. OFOTOKUN: Absolutely.

16 DR. BADEN: -- to choose A versus B --

17 DR. OFOTOKUN: Yes.

18 DR. BADEN: -- given what's known about A  
19 and what's unknown about B.

20 DR. OFOTOKUN: Absolutely.

21 DR. BADEN: Despite the small risk but a  
22 very serious one. Although in the India study,

1 they were able to do it, meaning it was doable, and  
2 then it's a small number.

3 Dr. Burgess?

4 CAPT BURGESS: Dr. Harrist's comment made me  
5 think about this. As a practitioner making a  
6 recommendation, I like 99.9 percent a lot more than  
7 I like 99.5 percent for sure, but this is for a  
8 U.S. BLA. I think our confidence in 99.9 percent  
9 is about canine rabies. I think our confidence  
10 about the effectiveness for other is just less  
11 because there's less experience. So I'm struggling  
12 with how to weigh that.

13 DR. BADEN: And I was struggling with the  
14 same issue, and I don't know if Dr. Moore or  
15 Ellison would want to comment. The 99.9 percent  
16 number for HRIG, how confident are we in that  
17 number for the kinds of rabies that we see in the  
18 U.S.? Because the whole discussion is predicated  
19 that that number is a fact, and does it have  
20 variability or other considerations that make it  
21 less certain?

22 DR. ELLISON: We have about 30,000 exposures

1 a year in the United States, 34,000-ish. There's  
2 no denominator. We haven't had a failure  
3 associated with HRIG in the United States,  
4 associated with all the different exposures that  
5 happen in all the states. That's the only thing I  
6 can tell you.

7 CAPT BURGESS: Not to take issue with that  
8 at all, but there are exposures and there are  
9 exposures, and there are recommendations to get  
10 post-exposure prophylaxis here that are different  
11 than recommendations to get post-exposure  
12 prophylaxis in other places.

13 DR. ELLISON: Absolutely, I completely  
14 agree.

15 DR. MOORE: From what I understand, that  
16 99.9 came from the Philippines, the large --

17 DR. BADEN: Dr. Troy, please?

18 DR. TROY: Actually, the Philippines would  
19 be 99.99 percent. The 99.9 was from the field  
20 trials, that there's lots of variability.

21 DR. MOORE: I consider the variability,  
22 especially in developing countries where deaths may

1 not be recorded to rabies, so I kind of take that  
2 into consideration, too. It is a number, but does  
3 it include everything?

4 DR. BADEN: Dr. Swaminathan? No? Okay.

5 Dr. Green?

6 DR. GREEN: Yes. I wasn't certain how many  
7 of the subjects or participants that are not  
8 getting the composite monoclonal need to get ERIG  
9 versus HRIG. The bullet that we're going to be  
10 voting on actually only mentions HRIG, so I wanted  
11 to clarify, as I've clarified earlier and as we've,  
12 that we need to have that be ERIG as well. But I  
13 don't know whether now you have to think about is a  
14 thousand adequate because then you only have 125 of  
15 each of those, or is it if you're in the United  
16 States and we're only doing 100 people or 50 people  
17 in the United States, they get HRIG, and if you're  
18 outside, you get it there, and how that impacts on  
19 comparability.

20 The data that you just quoted to us from the  
21 Philippines, is that with ERIG?

22 DR. BELL: In the Philippines, 96 percent

1 get ERIG free [indiscernible].

2 DR. GREEN: So when we go to vote, again,  
3 the question as posed we're voting on says HRIG,  
4 and it's going to be a caveat that it's not going  
5 to all be HRIG, and maybe very little bit is going  
6 to be HRIG, but we just have to take that into  
7 consideration and make that as a statement with the  
8 vote that we give.

9 DR. BELL: Can I talk? I'm sorry.

10 DR. BADEN: Yes, Dr. Bell?

11 DR. BELL: The discussion that we had  
12 internally was if it's for the U.S. s population,  
13 HRIG may be an appropriate comparator, but some  
14 people's opinions might be that ERIG should be  
15 done.

16 DR. GREEN: But does that imply, then, that  
17 if you're doing the study in Africa or India, that  
18 you're going to ask the sponsor to use HRIG because  
19 it's to get a U.S. indication?

20 DR. BELL: That's a good question. It  
21 significantly adds to the cost of the development.

22 DR. BADEN: Is it to the U.S. standard or is

1       it to what is the clinical standard, if you're  
2       trying to understand how the new therapy behaves?  
3       Because ultimately we want to understand how the  
4       new therapy behaves, which I would think would be  
5       related to the clinical standard rather than the  
6       local standard, local meaning just the U.S.

7               DR. BELL: We had discussion with ethicists  
8       at the public workshop, and some discussion was in  
9       areas where they have different access to therapy  
10      for that indication, for example, PrEP, it might be  
11      ethical to do what's the standard of that location.  
12      But if we were to approve this product for the U.S.  
13      population where they get HRIG, that's where some  
14      people were grappling with should the comparator be  
15      HRIG or HRIG versus ERIG.

16              DR. BADEN: Well, hopefully the  
17      breakthroughs will be close to zero, so it may turn  
18      out to be similar.

19              DR. BELL: I mentioned capturing the rabies,  
20      I looked back at the transcript from the public  
21      workshop, and the doctor from the Philippines said  
22      that in 2006, they got 200 animal heads, and 30

1 percent were diagnosed as being rabid. In the  
2 center, they have 3,500 exposures in 2016, so  
3 that's the ballpark of definitive rabies from the  
4 animal.

5 DR. BADEN: We have several follow-ons.  
6 We'll do Dr. Weina.

7 DR. WEINA: Again, whether we use HRIG or  
8 ERIG as the comparator would depend upon the entire  
9 package. So if the animal data showed that HRIG  
10 and ERIG were equivalent with the monoclonal, then  
11 would it really even matter in the clinical trial  
12 whether you use HRIG or ERIG, right?

13 DR. TROY: I think one issue, since HRIG is  
14 the only product approved in the United States in  
15 terms of the safety comparison, HRIG would be more  
16 relevant, I think, for approval in the U.S., even  
17 if ERIG is used more often globally.

18 DR. WEINA: And just makes getting 750 even  
19 that much harder for a sponsor.

20 DR. MOORE: If I remember from the 2017  
21 workshop, representatives from Taiwan, Thailand,  
22 and the Philippines made it pretty clear that in

1 their minds and their experience, ERIG and HRIG  
2 were equally effective, so there's that. Then  
3 also, if this study is done in other countries, are  
4 you going to accept the post-exposure prophylaxis  
5 vaccine schedule as far as route and days?

6 DR. MURRAY: I think with the ethics of  
7 research, though, we have to do somewhat of a  
8 clinical standard for the locale. We can't  
9 substitute something that that community won't get  
10 in the future, and then take it away. So for the  
11 data to also be applicable to them, we have to use  
12 I think the local standards. I think there's a  
13 principle related to that, an ethical principle,  
14 the way you would do research.

15 I think ERIG and HRIG are pretty similar.  
16 They appeared to be pretty similar when we looked  
17 at the clinical trials as far as failures. I think  
18 the difference might be more so in the safety and  
19 some of the adverse reactions. So I think there  
20 could be a recommendation for maybe using HRIG,  
21 where it's acceptable in that community, but I  
22 think clinical trials would have to be kind of

1 flexible to a clinical standard, and that's my  
2 opinion.

3 DR. BADEN: And you will have the failures  
4 in the novel treatment, which ultimately is going  
5 to drive the assessment. The  
6 absence of failures in the novel treatment makes it  
7 easy to compare to whatever you are comparing it  
8 to, and an overwhelming number of failures would be  
9 problematic.

10 DR. MURRAY: And I think the nuance, the  
11 difference between using ERIG or HRIG as a  
12 comparator kind of pales to the overall uncertainty  
13 we'll have with the amount of data.

14 DR. BADEN: I think Dr. Ellison had a follow  
15 on, and he's been patient.

16 DR. ELLISON: It was actually a question  
17 about the clarity. Will these animals be  
18 laboratory confirmed as being rabid?

19 DR. BADEN: Do you think that is feasible?

20 DR. ELLISON: It depends on where you're  
21 doing.

22 DR. BADEN: It sounds like in the

1       Philippines, they had less than 10 percent of the  
2       animals, and only a third of them were confirmed.  
3       And I assume where they brought the animals in,  
4       there may have been greater concern. I don't know.

5               I think it would be very advantageous to  
6       have it confirmed, have the animal, and really  
7       understand the exposure, and measure it from the  
8       distance from the CNS. I'm just not sure that that  
9       will be practical. But your point's very well  
10      taken, and I think that's the issue, is how much  
11      exposure is the exposure, and if there's even an  
12      exposure.

13             Dr. Kartsonis?

14             DR. KARTSONIS: I was just going to make one  
15      point about the ERIG versus HRIG. Actually, if the  
16      pharmaceutical company is going to go forward with  
17      this kind of study and would be providing the HRIG,  
18      that may actually be an opportunity to assist with  
19      recruitment in the sense that if ERIG is the  
20      standard of care or if these therapies are being  
21      paid for by the patient in these parts of the  
22      world, this may indeed be something that would help

1 with recruitment in terms of giving HRIG, and to  
2 say we normally use ERIG, but HRIG could actually  
3 be a safer option for you in that particular  
4 region. So it's a way to kind of get recruitment  
5 to help you.

6 DR. BADEN: Sure. That makes sense. I just  
7 am always leery if HRIG is not approved in that  
8 country.

9 DR. KARTSONIS: I don't mean --

10 DR. BADEN: One has to have certain -- and I  
11 don't know all the local nuance. But your point's  
12 well taken. If the sponsor of the study is  
13 bringing both sets of products free of cost --

14 DR. KARTSONIS: Absolutely.

15 DR. BADEN: -- as long as there's local  
16 acceptance of the comparator.

17 DR. KARTSONIS: Which obviously the ethics  
18 committee would have to approve and the local  
19 countries would have to approve as well.

20 DR. BADEN: And one would hope flexibility  
21 on the country, but also flexibility on the agency  
22 to be practical as long as the scientific data are

1 available to give confidence that what was assessed  
2 shows evidence of meaningful activity.

3 DR. KARTSONIS: That's right.

4 DR. BADEN: Dr. Gripshover?

5 DR. GRIPSHOVER: [Inaudible - off mic].

6 DR. BADEN: Dr. Ofotokun? No? Dr. Siberry?

7 DR. SIBERRY: So on this ERIG/HRIG, I think  
8 the mortality comparison, they can be combined. I  
9 really don't see the value in trying to stipulate  
10 it be all one or have separate subgroups.  
11 Mortality comparison, they should be combined.

12 I think it would be feasible to require that  
13 the sponsor have enough recruited to do the  
14 short-term safety outcomes and serologic analyses  
15 and vaccine interference for the HRIG comparator.  
16 That's going to be a subgroup. That's going to be  
17 feasible. So I think a hybrid approach where you  
18 require an HRIG comparator for some of those,  
19 that's a relatively smaller number to get at. But  
20 then for the efficacy, the mortality comparison,  
21 absolutely, either one, they should just be  
22 combined.

1 DR. BADEN: Dr. Porter?

2 DR. PORTER: I'm not sure that this is an  
3 issue that we're addressing, but I can see that  
4 there would be a difficulty in enrolling people for  
5 the trial, because rabies is 100 percent fatal. So  
6 the difference of 0.4 percent is real to patients.  
7 I had a low-risk cat bite and went through the  
8 whole series because there was this much chance.  
9 Though I was familiar with the colony the cat came  
10 from and everything else, I still went through with  
11 it.

12 I think even given the opportunity to have  
13 the monoclonal antibody, I would've chosen still  
14 the HRIG. This is reality because I think if it  
15 wasn't a fatal disease, 100 percent fatal, then  
16 there might be some play there, but there isn't.

17 DR. BADEN: Dr. Swaminathan?

18 DR. SWAMINATHAN: I just wanted to make sure  
19 I understood, how many patients got vaccine and PEP  
20 in the Philippines, did you say?

21 DR. TROY: I can tell you I think it's like  
22 3500 a year, who are WHO category 3 exposures and

1 got PEP including RIG. There were additional ones  
2 who were not WHO category 3, WHO category 2 that  
3 just got the vaccine, and then I believe there were  
4 some who didn't get the RIG.

5 DR. SWAMINATHAN: But it was like 3500.

6 DR. TROY: Yes.

7 DR. SWAMINATHAN: And the presumed  
8 prevalence there of actual rabid exposure is about  
9 10 percent?

10 DR. TROY: So, yes. It's a rabies-endemic  
11 country, but it's on the lower side, so I think it  
12 was around 10 or 15 percent, yes.

13 DR. SWAMINATHAN: But like the heads, it was  
14 like 10 percent, right?

15 DR. TROY: Yes.

16 DR. BELL: I think it was 200 heads and 30  
17 were -- 15 percent.

18 DR. SWAMINATHAN: But 10-15 percent or  
19 whatever.  
20 So there's really only about 1200 or something a  
21 year that had real exposure, likely to have had  
22 actual rabies exposure. So this number of 99.99

1 percent, what's the standard error of that?

2 DR. TROY: That's of the WHO exposures.  
3 That's not of people who were actually --

4 DR. FOLLMANN: I understand, but thinking  
5 about actual risk to people -- antibiotics work  
6 really well when you have a virus, so I like to  
7 think about situations where it actually might make  
8 a difference. So if in fact about a thousand  
9 people, it was successfully used and there were no  
10 deaths, does that really mean it's 99? Is it 99.5  
11 plus or minus?

12 DR. TROY: That's the crux of the question.  
13 You're right, because we don't have any good data  
14 on people where it's confirmed to be rabid and what  
15 the percentages are in those cases. We only have  
16 data where it's WHO category 3 exposure.

17 DR. SWAMINATHAN: Then the other question, I  
18 was under the impression that equine antibody had a  
19 significant risk profile, sort of adverse effects.

20 DR. TROY: It's improved recently. It used  
21 to have a very bad safety profile, and since  
22 they've done better purification techniques with

1 just the Fab fragments and things like that, and  
2 now that the rates are much lower. So I think  
3 there's still -- and you can correct me. I think  
4 they're still higher than with HRIG in general, but  
5 it's quite low. It's like 1 percent now for ERIG.

6 DR. BADEN: Dr. Follmann?

7 DR. FOLLMANN: I just wanted to summarize  
8 what I was thinking about the study that would be  
9 needed that would be voted on. I think it would be  
10 750 per arm, a randomized double-blind controlled  
11 study maybe with HRIG or ERIG, but that would be  
12 known by locality. So you could stratify the  
13 safety analysis by that, as Dr. Siberry was saying,  
14 but mortality would be looked at overall.

15 We had talked earlier about the issue of  
16 exposure and other factors that might impact the  
17 risk of mortality and feel that it could be  
18 challenging to get that, but I do think we should  
19 try to collect that as best we can, including time  
20 from exposure if you can genotype the virus that  
21 infected or exposed to the human; location of the  
22 bite, species, and those sorts of things. I think

1 that should be part of both the 750 trial and the  
2 6,000-person trial.

3 Also, the WHO category seems great for  
4 decision-making or some kind of risk, but I don't  
5 know if it really relates to whether you've been  
6 exposed to the virus, and maybe there'd be another  
7 way to collect data or have a different or better  
8 risk category than WHO has, some that would take  
9 into account it wasn't just a dog bite, but you  
10 could sacrifice the dog and see that it was, or  
11 something like that. So there could be an  
12 opportunity to better risk stratify than just the  
13 WHO categories.

14 The other thing is just a comment. There's  
15 been discussion about it might be hard to recruit  
16 for monoclonal antibody because it's new, but it's  
17 been approved in India, so it's possible there  
18 would be a lot of experience with the Indian  
19 monoclonal, especially if it's competitively priced  
20 or disseminated by the government or something. So  
21 that could remove the challenge in recruiting for  
22 the studies we're talking about.

1 DR. BADEN: And that's part of how KEDRAB  
2 was approved, based upon leveraging other data, and  
3 that's polyclonal. So your point's well taken. I  
4 just want to push you a little bit on the 750  
5 number. What do you think of the 750 number as the  
6 efficacy marker and the thousand number as the  
7 safety marker?

8 DR. FOLLMANN: I was glad the FDA proposed a  
9 number and then sort of a concede [indiscernible]  
10 to choose that or not. It's like we use p 0.05,  
11 and I'm glad I don't have to rethink that every  
12 meeting. But the 750 is tied to the 99.5, so that  
13 seems like a reasonable green light on the path to  
14 a larger study. That's sort of the end of my  
15 thinking about it, but it's predicated on the idea  
16 we do the 750 study, and then we get the 6,000  
17 study, and then maybe that would be more widely  
18 used, and then we could get more data. So a  
19 graduated approach to information.

20 That's my view on the numbers for mortality.  
21 The thousand on safety, I guess that's a common  
22 number the FDA uses for safety, and I have no

1       dissension from that.

2               DR. BADEN:  And the 750 on the way to  
3 approval and then the 6,000 in the postmarketing  
4 category doesn't seem unreasonable to you in a  
5 graduated approach?

6               DR. FOLLMANN:  No, that seems reasonable.  
7 Importantly, it's 750, the approval for this is a  
8 second-line therapy.

9               DR. GREEN:  Dr. Follmann, can you just  
10 restate that algorithm that you did.  I just want  
11 to make sure I understood because you spoke quick,  
12 but I always like to pay attention.

13              DR. FOLLMANN:  I was thinking with 750, if  
14 there's no mortality, we can know that survival is  
15 99.5 or better.  That seems like a reasonable  
16 signal to turn on the green light to a  
17 postmarketing study and a licensure that says the  
18 monoclonal would be used as a second-line therapy,  
19 so that would incentivize or make it more likely  
20 that we would get the postmarketing study, and then  
21 we'd have presumably that information.  And if no  
22 one died in the 6,000 in the monoclonal, then we

1 would say survival is 99.99 or better, which is I  
2 think good evidence for wide use of it.

3 So it's sort of predicated on winning on  
4 mortality each time, but that's --

5 DR. GREEN: And the comparator, was that 750  
6 as the comparator?

7 DR. FOLLMANN: Yes. I was thinking, as FDA  
8 suggested, 750 in the initial study, premarketing  
9 study, as a kind of reference but not a formal  
10 comparator because we expect very, very low  
11 mortality. It's sort of a canary in the coal mine  
12 or some kind of control for that. And then in the  
13 postmarketing study, they were suggesting a 2 or 3  
14 to 1 randomization. So 6,000 on the monoclonal  
15 antibody and 2000, say, on the comparator, which  
16 also seemed reasonable to me.

17 DR. BADEN: And this study of course needs  
18 to be done where high-risk exposures are present.

19 DR. FOLLMANN: Yes. It's all sort of  
20 predicated on that. I worry a bit about if the  
21 U.S. -- like in Virginia if you get bit by a dog  
22 and you're going to be a high category, that has to

1 be thought of carefully.

2 One other comment. In some of the  
3 information, it was saying we could use the 750 as  
4 part of the 6,000, and I don't think you should. I  
5 think you should do 750 and then do a fresh 6,000  
6 because I don't want to double-count. It just  
7 seems better to have a complete independent set of  
8 data to get a clear signal.

9 DR. GREEN: That's a modification of bullet  
10 B. That's just the reason why I was getting a  
11 clarification. Bullet B is written as 750  
12 participants get the polyclonal -- or bullet  
13 B/C -- and at least a thousand subjects  
14 get -- versus HRIG and at least -- actually I'm  
15 confused as to what FDA was saying now.

16 Were they proposing 750 versus a 250  
17 comparator or 750 versus a thousand?

18 DR. TROY: Sorry. So at least 750 who  
19 receive the mAb cocktail, who were rabies exposed  
20 in rabies-endemic countries, but then at least a  
21 thousand who receive the mAb cocktail overall,  
22 including phase 1 subjects who were healthy

1 subjects who weren't exposed, because a thousand  
2 would be for the safety; the 750 would be --

3 DR. GREEN: So you didn't mention in your A,  
4 B, and C what would be the comparator size.

5 DR. TROY: We didn't mention.

6 DR. GREEN: Thank you.

7 DR. BADEN: But the 750 in the C could  
8 contribute to B. And if there were those who were  
9 exposed but deemed to be category 1 or 2, they  
10 might go into safety but not count as much towards  
11 efficacy. So you don't have to have 2,000. It  
12 could be a more modest number since 200 was  
13 difficult.

14 Dr. Weina?

15 DR. WEINA: Thanks. I'm kind of struggling  
16 a little bit and hope to get people's thoughts on  
17 the idea of approving it as a first-line indication  
18 versus a second-line indication, especially in  
19 light of a lot of these numbers, we're just kind of  
20 fooling ourselves, really. I mean, because,  
21 honestly, surveillance in the United States for  
22 rabid animals have consistently bounced around only

1 5[000] 6,000 animals when they're actively  
2 surveilling animals in the entire country for the  
3 entire year, and usually between 1 in 4 or 1 in 5  
4 max, human cases in the U.S. every year. And yet  
5 we give -- just at Fort Belvoir gives tons of  
6 post-exposure prophylaxis for rabies all the time.

7 So if we're going to be saying it's a  
8 second-line indication, do we ever expect in any of  
9 our lifetimes to ever actually get 6,000  
10 rabies-exposed people in postmarketing  
11 surveillance? The thing is, postmarketing  
12 surveillance --

13 DR. BADEN: I guess my comment would be  
14 250,000 received a non-approved agent elsewhere in  
15 the world.

16 DR. WEINA: Elsewhere in the world, but for  
17 approving it in the United States, that doesn't  
18 mean it's going to be approved elsewhere.

19 DR. BADEN: No.

20 DR. WEINA: And we're not going to do  
21 clinical trials elsewhere after it's been approved.

22 DR. BADEN: No, but that was approved in the

1 U.S. based upon data from elsewhere --

2 DR. WEINA: Right.

3 DR. BADEN: -- and I think that if the  
4 question is what's an amount of data to allow  
5 approval, I think your point is fair, is that is it  
6 first or second line? And then the question is how  
7 do additional data get generated and where, but  
8 that's more in the postmarketing.

9 DR. WEINA: No, I understand. But it kind  
10 of ties together because if we're going to sit  
11 there and say, well, yes, 750 is fine for  
12 second-line indication in the United States. But  
13 we're talking about approval in the United States,  
14 so the postmarketing surveillance, at least the  
15 assumption we have to go by right now is that it's  
16 going to be 6,000 from the U.S. unless other people  
17 approve it as well.

18 DR. TROY: Sorry. It wouldn't be 6,000 in  
19 the U.S. It actually would be 1 to 6,000 in  
20 rabies-endemic countries. So it'd be a  
21 postmarketing requirement, but it would not be done  
22 predominantly in the U.S.

1 DR. BADEN: The requirement would be where  
2 they're highly exposed, but that would require  
3 those environments supporting its use in those  
4 environments.

5 DR. WEINA: Right.

6 DR. BADEN: Dr. Siberry?

7 DR. SIBERRY: We're having postmarketing  
8 discussions; that's the next point, so I hope we'll  
9 come back to that as a separate topic. Two quick  
10 things. We're talking about FDA potentially having  
11 a second-line indication, and I just wanted to  
12 confirm that that was what would be in a label as  
13 opposed to what a guidelines group would do. That  
14 sounds like guidelines terminology to me.

15 DR. GREEN: It could be in a label.

16 DR. SIBERRY: Could it be labeled that way?

17 DR. MURRAY: Well, it could be. Anything  
18 could be done in a label. I just don't know what  
19 second line necessarily means in this case. It  
20 could be based on the type of exposure, the type of  
21 bite, single bite. It could be a category 3 that  
22 you thought was otherwise kind of low risk. Is

1 that what you mean by second line, only if HRIG  
2 isn't available? That's one other kind of second  
3 line. That's a whole another discussion, what is  
4 your definition of second line?

5 DR. BADEN: That's really helpful.

6 DR. SIBERRY: Again, I feel like often  
7 guidelines groups will be thinking about what the  
8 clinician in the field and the health departments  
9 are doing and help put that in perspective of here  
10 are the places that you would use this compared to  
11 the other. I don't know that that's necessarily  
12 has to be in the label.

13 The other quick comment I have is I thought  
14 the thoughtful point by Dr. Porter about who's  
15 really going to accept this, we work with a group  
16 who are trying to study a way to get away from  
17 HBIG as part of hepatitis B perinatal transmission  
18 because access cost was really difficult in this  
19 lower income country.

20 So the group worked with the Ministry of  
21 Health in that country, who was struggling also  
22 with how do they increase access to an alternative

1 that might hopefully be as good but would be either  
2 cheaper or more feasible. So I think the sponsor  
3 should be encouraged to work with ministries of  
4 lower and middle income countries where rabies is  
5 not only a big problem, but where access to the  
6 equine or the human immunoglobulin is a major  
7 problem because that I think is where you get the  
8 equipoise and then the ability to kind of go into  
9 an area with the ministries' support to offer  
10 something that will be a prospect of benefit to all  
11 participants who otherwise wouldn't have any  
12 access.

13 So just as a recommendation that this is an  
14 important thing to have the sponsor work in  
15 coordination with ministries of countries who are  
16 faced with that dilemma.

17 DR. BADEN: Point well taken. I think we're  
18 not going to solve all the ethical challenges. I  
19 think the fact that there are 60,000 deaths  
20 annually, there's an unmet need that this can  
21 potentially contribute to solving. But the  
22 sponsor, with whatever product is emerging, is

1 going to have to struggle with this, and struggle  
2 with the communities that are relevant, that's in  
3 an ethically appropriate manner, and that's  
4 assumed. But how to define that will have to be  
5 defined 1 year, 5 years from now when the facts are  
6 available, but the ethics will have to be addressed  
7 in a very thoughtful way. But there clearly is an  
8 unmet need, and perhaps this can help address that  
9 in some small way.

10 We have to get to voting shortly, so I'm  
11 going to ask that comments be pithy, and then there  
12 may be a couple of pointed issues that I want us to  
13 address before we vote.

14 Dr. Burgess?

15 CAPT BURGESS: Hopefully a pithy question,  
16 but back to Dr. Follmann. I just want to clarify,  
17 when you were describing the 750 versus 750, you  
18 said double-blinded. I just want to ask the folks'  
19 thoughts about the importance of allocation masking  
20 in the context of a rabies post-exposure study.

21 DR. BADEN: That was one of the issues I was  
22 going to focus in on, so thank you.

1 Dr. Follmann, do you wish to comment?

2 DR. FOLLMANN: Just for the generic reasons,  
3 we like blinding, so the participant will know they  
4 got a blinded product as opposed to the new thing  
5 versus the reliable thing. I don't know the  
6 specific scenarios why that would cause necessarily  
7 a particular problem other than it's just good  
8 clinical trial practice. I would think it'd be  
9 relatively easy to blind in the study relative to  
10 like other things, I could imagine, but I really  
11 don't know how easy blinding would be.

12 CAPT BURGESS: I think it might actually be  
13 practically difficult in certain circumstances  
14 because of the volume of the product, for example,  
15 and you could get around that. But the question  
16 really is, from a statistical perspective, from an  
17 hypothesis testing perspective, is that important?

18 DR. FOLLMANN: I guess it's less important  
19 for mortality where it's harder to imagine how lack  
20 of blinding would have an impact. Maybe for safety  
21 it is more important. Maybe safety studies in  
22 controlled populations where it's easier to

1 administer, you could double-blind and maybe in the  
2 field less, so we are focusing on mortality. I  
3 don't want to be dogmatic and say it has to be  
4 double-blinded. I was just imagining that would be  
5 the gold standard, but there might be practical  
6 issues with it. But mortality as an endpoint is  
7 hard to see how it would be impacted.

8 DR. BADEN: Dr. Kartsonis, did you have a  
9 comment?

10 Others? Because I think a critical point  
11 that we're being asked is what do we think of the  
12 750 and what do we think of the study design, and  
13 whether it's a double-blind or open-label, given  
14 that it's a mortality endpoint for the efficacy,  
15 not for the safety, because I think the safety will  
16 get much harder to understand in an open format.

17 Anyone have strong views on should there be  
18 a comparator or not? I think Dr. Kartsonis earlier  
19 said the value of a comparator is to deal with the  
20 noise of the situation, particularly if the  
21 exposure amount is so variable that it's going to  
22 be hard to know what the background should be.

1 DR. GRIPSHOVER: That's actually what I was  
2 going to -- why I had my card up to clarify is that  
3 what we're voting on, because I strongly think we  
4 should have a comparator because I think if there's  
5 an outbreak of more rabid animals, we don't want it  
6 to mess it up. So I definitely think the 750  
7 should be in a comparator study.

8 So part of my question is, is that what  
9 we're going to be voting on? Question C, is that  
10 750 a randomized trial of H/equine RIG versus our  
11 new drug? I guess that's for the FDA or not, if  
12 that's what they're asking us.

13 DR. BADEN: The way I'm hoping to frame the  
14 vote, and the agency can chime in, is do we, each  
15 of us, think that if the BLA package had a safety  
16 element and efficacy element, would that be  
17 adequate for approval? The safety element proposed  
18 has a thousand subjects or participants for safety,  
19 and the efficacy is 750, is what they're proposing.

20 If you think that this could be adequate,  
21 you're allowed to say it should be 1500; it should  
22 be 200; that this is a path that makes sense; the

1 numbers are too high or too low, as a sense of  
2 confidence for the initial approval, and then  
3 whether or not you think that would be adequate for  
4 first line or second line. And I apologize to the  
5 agency that that's not defined for the label, but I  
6 think it will be important for is this adequate  
7 efficacy and safety that one could imagine it being  
8 used.

9           Then whether it's in the label or in the  
10 practice guidelines, that will work itself out  
11 because the community will know the data. But  
12 would this be adequate for an approval with all of  
13 the caveats we've been discussing, and then we can  
14 always say there should be bigger numbers, and we  
15 can leave that to the postmarketing discussion, but  
16 adequacy for approval.

17           If no objections from the agency, I'll be  
18 framing the question that way for the group. And  
19 in your yes/no discussion, succinctly comment on  
20 safety adequate, bigger, smaller; efficacy  
21 adequate, bigger, smaller; first line, second line.  
22 If you say no, then add in what's missing that

1 would be critical for a BLA to be seriously  
2 considered. We're not getting to the vote just  
3 yet, but I've framed the question.

4 Dr. Ofotokun?

5 DR. OFOTOKUN: One thing. Should that be  
6 really a question for us rather than it should be  
7 for -- if we agree that this should go forward,  
8 then they should get their statistician and  
9 clinical trial designers to work out the  
10 appropriate number that is needed. I don't know if  
11 that should be a question that we should address.

12 DR. BADEN: Your point's well taken, which  
13 is any specific application will be predicated on  
14 the details of that application. What I think I  
15 hear from the agency in the document and the  
16 presentation is, is there a roadmap of what an  
17 approval could look like, and is there is a roadmap  
18 that could lead to an approval with 101 details  
19 associated with the specifics of the product and  
20 the advantages or disadvantages of the product, or  
21 is it impossible to even consider a path to  
22 approval?

1           That's what I'm hearing, is that is there a  
2 path to approval? Of course I don't see us  
3 advocating this is set in stone; this is the  
4 answer. For a generic product that doesn't have  
5 anything special of concern, would this be a  
6 reasonable path to say that we could see approval  
7 with all of the postmarketing?

8           So I think the follow-on to approval would  
9 be critical, but you have to at least get over that  
10 first bar and say are there enough data to consider  
11 that this is a path to approval, realizing 5 years  
12 from now, the details of the product will guide the  
13 discussion and any other new science that emerges.

14           But I hear that that's the guidance the  
15 agency's looking for because, otherwise, developers  
16 don't even know where to begin to think about what  
17 path do we take to even begin to develop. And  
18 there I think we do want to encourage the community  
19 to think about developing new therapies for  
20 diseases that I don't think we're satisfied are  
21 adequately addressed globally.

22           Other key discussion points? I know

1 Dr. Swaminathan -- I'm easily fooled by the  
2 misaligned cards. So are there other key  
3 discussions? If not, the points that I wanted to  
4 highlight I think were highlighted, but does anyone  
5 want to comment on the thousand participants is  
6 adequate safety? Anyone have other comments about  
7 the 750 is adequate efficacy for the BLA? Do we  
8 need any other pointed discussion on that? Because  
9 I agree with Dr. Follmann, I am glad that the  
10 agency put out a straw man there because it is  
11 arbitrary, but it does have a rationale that makes  
12 sense, given the state of the data in this space.

13 Dr. Siberry?

14 DR. SIBERRY: Just briefly since it came up  
15 before, yes, that thousand makes sense, but we  
16 should explicitly say it should include children  
17 and pregnant women, and those will come in after  
18 some preset number go through the safety study. So  
19 I just want to make sure that they're explicitly  
20 considered in the group who have safety data  
21 collected.

22 DR. BADEN: What I would ask is that the

1 question before us will be is this a roadmap that  
2 makes sense? Then if there are key considerations  
3 like that, add that in your footnote. If you vote  
4 yes, if you vote no, please explain why you think  
5 there's a key element missing. But that would be  
6 part of the -- and how much of that is in the BLA  
7 element versus how much of that is in the  
8 postmarketing, given the requirements for the BLA  
9 and how you can expose children without benefit.

10 So I want to be sensitive to other  
11 regulations that have to be thought about as data  
12 are being accrued, but ultimately that would be  
13 necessary.

14 So if there is no other discussion on those  
15 key elements of the proposal, then we can move to  
16 vote. The vote on this will be yes, a package with  
17 this kind of information, and you can give comments  
18 on higher or lower numbers or this is reasonable,  
19 and comments on the first line, second line; no,  
20 and why no?

21 So would a data package containing the  
22 following additional information be sufficient to

1 support submission of a U.S. BLA, comparable RVNA  
2 levels and vaccine interference with a mAb cocktail  
3 versus HRIG or ERIG in a clinical trial of  
4 rabies-exposed subjects; comparable safety profile  
5 of the mAb versus HRIG or ERIG in at least a  
6 thousand subjects or participants; lack of  
7 mortality in at least 750 participants with  
8 increased risk of exposure.

9           If yes, would the described data package  
10 support first-line indication for use as part of  
11 PEP or a second-line indication such as when HRIG  
12 is not available? If no, what other elements would  
13 you want for a BLA to be considered? So yes, no,  
14 abstain.

15           May we begin the voting?

16           (Voting.)

17           DR. BADEN: We are a consistent lot: 16,  
18 yes; zero, no; zero, abstaining; zero, no voting.  
19 We will start on the left with Dr. Swaminathan. We  
20 have limited time because we still need to discuss  
21 the postmarketing. We already touched on that.  
22 But if when you affirm the way you voted, if you

1 can give whatever key elements associated with the  
2 adjunct comments I mentioned, that would be  
3 appreciated.

4 DR. SWAMINATHAN: I voted yes. Should I  
5 answer this question about the first-line  
6 indication?

7 DR. BADEN: Yes.

8 DR. SWAMINATHAN: I would say that I would  
9 be in favor of it being for a second-line  
10 indication such as when HRIG is not available and  
11 also to have exclusions for high-risk cases and  
12 situations in which the efficacy may not be  
13 generalizable, based on differences from the study  
14 population versus the broad indication as a first-  
15 line therapy for all types of cases.

16 DR. BADEN: That was Dr. Swaminathan.  
17 Please state your name, and then your vote, and  
18 then the comment.

19 DR. SIBERRY: George Siberry. I voted yes.  
20 I'll just add that I think that the initial studies  
21 should make sure to strictly limit inclusion to  
22 those who present within 72 hours of a bite. When

1 there's a bite, that's the reason to keep things  
2 somewhat similar. After an initial phase, when  
3 enough data are collected within the context of  
4 this study in adults, it is absolutely ethically  
5 and regulatorily appropriate to include children,  
6 and I would also say to consider including pregnant  
7 women at that point.

8 Finally, I will re-express my skepticism  
9 that we get meaningful information from 750 people  
10 who don't die when they get the alternative, with  
11 the current standard of care. That comparison  
12 provides relatively little information. Thank you.

13 DR. BADEN: Dr. Gripshover?

14 DR. GRIPSHOVER: I voted yes, and I actually  
15 do think we should have a randomized trial of the  
16 two groups. And I would actually encourage  
17 engagement of communities that are not accessing  
18 either the new product or the rabies immune  
19 globulin currently where there's obviously still a  
20 huge need since we have 60,000 people dying of  
21 rabies. Regarding the label, I would suggest that  
22 we include to use it where HRIG is not available

1       until we get further results in the postmarketing  
2       study.

3               DR. BADEN:   Dr. Green?

4               DR. GREEN:   Michael Green.   I voted yes.   I  
5       think there's a need to define whether the  
6       comparator group will receive HRIG versus ERIG, and  
7       what that might imply in terms of number of  
8       participants receiving each of these alternatives  
9       if one or both are used.   I support the inclusion  
10      of 750 recipients of the monoclonal cocktail and  
11      750 recipients of either HRIG, or ERIG, or a  
12      combination therein.   I do feel that children and  
13      perhaps pregnant women should be included at some  
14      point after an interim safety analysis of the trial  
15      in exposed individuals and the prior normals prove  
16      the safety.

17              If the study is powered to affirm a 99.5  
18      percent survival, I would approve it with a plan on  
19      the label as a second-line therapy when HRIG is not  
20      available in the United States, and I would want  
21      the label to actually include the reasoning behind  
22      this level of approval compared to the equivalent

1 first-line therapy. When we get the postmarketing  
2 studies and data, I would hope that this eventually  
3 might evolve to equivalency and an upgrade to a  
4 first-line indication. Thank you.

5 DR. BADEN: Dr. Weina?

6 DR. WEINA: Peter Weina. I voted yes,  
7 assuming my second crystal ball is working inside  
8 of my first crystal ball. I say that because I  
9 agree we need a pathway to be laid out for sponsors  
10 to move the thing forward, but the reality is that  
11 this is all assuming that the cell culture data,  
12 and then the animal challenged data, and the  
13 healthy individual data is absolutely pristine and  
14 everything looks absolutely beautiful and nice.  
15 But when we're sitting here or our counterparts are  
16 sitting here 10 years from now, actually listening  
17 to the actual presentation on it, they're going to  
18 look at it and say 750 subjects are so much  
19 variability. How can we just do it with 750  
20 subjects? There's no way we can approve it, and  
21 everyone will vote no.

22 I would echo the issue that we need to have

1 on the label -- if this is a pathway that's going  
2 to go forward, that it's going to be for a  
3 second-line indication only if the HRIG is not  
4 available. Again, state actually clearly in the  
5 label why it's listed as a second line and why it's  
6 being approved at all. I think that would help  
7 with the approval for it.

8 DR. BADEN: As time is short, Lindsey Baden.  
9 I voted yes. I think that a thousand seems  
10 reasonable; 750 seems reasonable. I favor also the  
11 comparative trial with local standard in the  
12 international environment; and second line, based  
13 upon these data, required postmarketing, and then  
14 the postmarketing would allow us to elevate our  
15 confidence in its activity.

16 Dr. Clark?

17 DR. CLARK: Nina Clark. I voted yes. I  
18 also think using as many trials sites as possible,  
19 where RIG isn't given routinely, is the ideal. I  
20 accept the rationale for the numbers proposed for  
21 participants as assurance that a larger studies  
22 should be done, and then agree with the second-line

1 designation, particularly HRIG is unavailable until  
2 more data are available.

3 DR. BADEN: Dr. Follmann?

4 DR. FOLLMANN: I voted yes. I think I gave  
5 my reasons before. I think the thousand and the  
6 750 randomized to a comparator is important. I  
7 think it should be used for a second-line  
8 indication when the HRIG is not available.

9 DR. BADEN: Dr. Ofotokun?

10 DR. OFOTOKUN: Igho Ofotokun. I voted yes  
11 for many of the reasons that have been expressed.  
12 I think the numbers 750 and thousand is set quite  
13 adequate. I also agree with the second-line  
14 designation until additional information is  
15 available. I would also reiterate that it will be  
16 important that as safety data becomes available,  
17 that we should enroll diverse population, women and  
18 children, older age group, so that we know how this  
19 drug works in these different population groups.

20 DR. BADEN: Dr. Burgess?

21 CAPT BURGESS: Timothy Burgess. I voted  
22 yes. I concur with the proposed rationale for the

1 numbers and occur with the comments that have been  
2 articulated about encouraging the inclusion of a  
3 diversity of populations. I would favor a trial  
4 design that involved a comparison with local  
5 standard of care, and concur with second-line  
6 indication.

7 DR. BADEN: Dr. Porter?

8 DR. PORTER: Laura Porter. I agree with  
9 what has been said before. I voted yes. I believe  
10 that second-line application if HRIG is not  
11 available and also to be consistent with the local  
12 standard of care.

13 DR. BADEN: Dr. Baker?

14 DR. BAKER: Judith Baker. I voted yes. I  
15 concur with the previous comments regarding local  
16 trial, local standards, age diversity, pregnant  
17 women, children, and older ages.

18 DR. BADEN: Thank you. Dr. Harrist?

19 DR. HARRIST: Ally Harrist. I voted yes.  
20 The numbers seem reasonable to me. I agree with  
21 including a diverse population and think that it  
22 should be second line.

1 DR. BADEN: Dr. Ellison?

2 DR. ELLISON: James Ellison. I voted yes.  
3 I agree the 750/1000 is a good number. They should  
4 use a diverse population, including children and  
5 second line.

6 DR. BADEN: Dr. Moore?

7 DR. MOORE: I voted yes. This is Susan  
8 Moore. I agree it should use the local standards  
9 of post-exposure treatment, and I think it should  
10 exclude high-risk bites, exposures.

11 DR. BADEN: Dr. Brown?

12 DR. BROWN: Catherine Brown. I voted yes.  
13 I agree with the rationale behind the proposed  
14 numbers. I agree with having a local comparator  
15 group, range of ages and both genders, and approved  
16 for a second-line indication.

17 DR. BADEN: Thank you. So I think we have a  
18 lot of consensus in our comments. Some additional  
19 comments by individual members, but largely  
20 consensus that there is a path forward here.

21 The final discussion element is  
22 postmarketing studies. There is no vote associated

1 with this. It's just a discussion. We have about  
2 10 or 15 minutes.

3 What are the key elements for postmarketing  
4 studies? If I heard everyone's tone properly, I  
5 think we all agree that that's a must, so it's a  
6 required element. The number put out there is  
7 6,000. And the next phase, the 6,000 to get to  
8 99.9 percent seems reasonable. It's a straw man,  
9 but it's a reasonable straw man. Again, the  
10 250,000 in the other study is always more  
11 attractive, but one has to do it step-wise as you  
12 incrementally develop data.

13 What key elements in the postmarketing study  
14 would members of the committee think to be  
15 critical? Diversity, I'll put 6,000 out there  
16 cause that's proposed, seems reasonable to get to  
17 the 99.9 percent. What other elements should be  
18 considered in the postmarketing element?

19 Dr. Burgess?

20 CAPT BURGESS: I think for a U.S. BLA, no  
21 disagreement with the number for 6,000, but I think  
22 a key element should focus on assessment of

1 exposures in the United States because the  
2 licensure package is going to be based on  
3 effectively canine rabies. That to me heightens  
4 the importance of close attention to non-canine  
5 rabies potential exposures.

6 DR. BADEN: As part of that, I think it is  
7 very hard to capture the virus associated with an  
8 exposure because we can't even sort out if an  
9 exposure occurred. However, if there's a failure,  
10 one would be able to look at the failure very  
11 intensely to understand any potential relationship  
12 with the intervention.

13 CAPT BURGESS: But there's usually a  
14 clinical indication for the post-exposure  
15 prophylaxis, which would infer the likely --

16 DR. BADEN: Of course.

17 CAPT BURGESS: -- the seriousness, if the  
18 exposure occurred at all.

19 DR. BADEN: Correct. Absolutely.

20 Dr. Green?

21 DR. GREEN: A comment and a second comment.  
22 I think it would be hard to get many of those 6,000

1 in the United States if they label it as a  
2 second-line indicator unless we actually have a  
3 shortage. Should there be a shortage in the United  
4 States, we should definitely be very aggressive  
5 trying to capture those information.

6 Having said that, what we could do is if  
7 it's being used in geographic variable locations  
8 outside of the United States, whether it's Africa,  
9 India, the Philippines, et cetera, we should try to  
10 get diverse utilization outside of the United  
11 States to get a sense of range of its  
12 protectiveness.

13 I they should definitely -- in their post  
14 exposure, it's a good opportunity to look at the  
15 variances of age to see if it's difference in those  
16 that might be limited in the original study but  
17 getting a lot of kids, getting a lot of elder  
18 individuals, and if they haven't got very many  
19 pregnant women and it was used to look at it in  
20 pregnant women. So really, an opportunity to  
21 enhance our understanding of the areas that might  
22 have been more limited in the original trial.

1 DR. BADEN: Dr. Ofotokun?

2 DR. OFOTOKUN: I think it's also an  
3 opportunity to look at how effective this product  
4 will be in individuals that are immunocompromised,  
5 which we have not really talked about. And there  
6 will be a broad range of immunocompromised  
7 individuals, particularly in a resource-limited  
8 setting that will be primarily HIV-infected  
9 individuals.

10 DR. BADEN: And in that setting, would you  
11 look at that as more of a healthy volunteer study  
12 versus a post-exposure study to make sure the  
13 kinetics of the intervention behave the same way in  
14 that population?

15 DR. OFOTOKUN: Because of the safety  
16 concern, it would be probably postmarketing people  
17 who really need it and then have an opportunity to  
18 really study whether it's effective and safe in  
19 that setting, rather than expose people who don't  
20 need it to a product that will show how they're  
21 going to react to it.

22 DR. BADEN: Because I think how well it

1 works in special populations --

2 DR. OFOTOKUN: Yes.

3 DR. BADEN: -- will be important.

4 Dr. Swaminathan?

5 DR. SWAMINATHAN: There are just a couple of  
6 issues that I see. One is that if it's marketed as  
7 labeled, which we pretty much agreed it would be a  
8 second-line indication, then the conclusions that  
9 can be drawn from postmarketing studies of that  
10 population will be limited by the fact that it will  
11 be a unique population where standard medical care  
12 is not available for either economic or political  
13 reasons. So it's going to be then given where HRIG  
14 is not available or current standard of care is not  
15 available.

16 Then the other --

17 DR. BADEN: Is that good or bad? I'm not  
18 sure I fully understand your comment.

19 DR. SWAMINATHAN: Well, for example, let's  
20 say that the characteristics of exposure and  
21 medical care, adequacy, and consistency of PEP may  
22 all be not representative of what would obtain

1 under better circumstances. So results could  
2 potentially be worse than under ideal  
3 circumstances, and that population may -- one would  
4 have to look at the data from such postmarketing  
5 studies with the realization that this is not a --

6 DR. BADEN: The generalizability. The  
7 population will have certain characteristics that  
8 are selected for, and that will have to be managed  
9 in the interpretation of the data.

10 DR. SWAMINATHAN: The other thing is -- and  
11 this has to do with what Dr. Green was talking  
12 about, is that short of a bat invasion in this  
13 country, it's unlikely that there will be much  
14 usage because there will not be a situation where  
15 HRIG is not available.

16 So I would think that even though there's a  
17 path forward that we've mapped here, that will be a  
18 very short path without much likelihood of at least  
19 immediate expansion into non-first-line indication  
20 populations.

21 DR. BADEN: The presumption there is that  
22 the U.S. is the primary space of interest.

1 DR. SWAMINATHAN: No. I'm just saying that  
2 the way this is mapped, it may never -- or it's  
3 difficult for me to envision a scenario where the  
4 postmarketing studies would provide enough  
5 additional further confirmation of its  
6 applicability in the U.S.

7 DR. BADEN: I guess I'm struggling with the  
8 issue of if one uses this intervention in high-risk  
9 individuals, wherever they are in the world, and  
10 the rabies breakthrough is very, very, very small,  
11 wouldn't that be reassuring, even though it's not a  
12 single U.S. person for argument's sake?

13 DR. SWAMINATHAN: Well, first of all, I'm  
14 not sure that -- I guess they would be high-risk  
15 people in places where the first-line therapy was  
16 not available.

17 DR. BADEN: What's driving my thinking is  
18 not that we can resolve it, but if I'm a sponsor, I  
19 would say there are 59,000 people who died this  
20 year with rabies. Let me figure out how to push  
21 this into those spaces where whatever is going on,  
22 those are untreated. And those 59,000 people are

1 not all the exposed. All the exposed is probably a  
2 million of which 59,000 were really exposed and  
3 died.

4 So that is not something we can solve, but I  
5 see that as a path for a sponsor to say there's a  
6 development path here because there's an unmet  
7 need. And if we're able to get into those spaces  
8 and show that it works, the 750 will be let's say  
9 in an RCT. The 6,000 may be uncontrolled. It's  
10 really a case series. But in the case series, if  
11 the characteristics are high enough risk, then  
12 might that be some evidence that there's activity?  
13 Then it all will depend on the adequacy of  
14 capturing failure, which is going to be a very  
15 tricky issue in a non-rigorous clinical trial.

16 DR. SWAMINATHAN: My concern isn't that -- I  
17 think the postmarketing follow-up, where it's  
18 given, under this labeling indication, will provide  
19 further confirmation of its safety and efficacy,  
20 and so forth. But it will not provide, at least  
21 not very soon, any evidence that that data on  
22 canine rabies in India applies to the type of

1 exposure and rabies that we have in this country.

2 DR. BADEN: No, that --

3 DR. SWAMINATHAN: Because, again, I say to  
4 you, you have been exposed by a bat. I can either  
5 give you HRIG or I can give you this other thing  
6 that works in other countries and other kinds of  
7 rabies, but we don't know how well it works with  
8 bat rabies.

9 DR. BADEN: But it's also very hard to  
10 interpret it in the U.S. data because we don't  
11 really understand any of the exposure. And the  
12 exposure is, I saw a bat. The exposure is  
13 incredibly variable, and I know in my state it  
14 wasn't even I saw bat; it's some kid brought a bat  
15 into school that was nailed on a board for show and  
16 tell, and was that an exposure?

17 So I think that it gets very hard to define  
18 exposure, and that was a complex discussion in our  
19 state.

20 Time is short. Yes?

21 DR. BELL: Sometimes things get used off  
22 label. Though we can't say that at the FDA, but

1 that's an opportunity for data. Like Dr. Harris  
2 brought up, maybe it's an option that's better than  
3 not having HRIG for some people.

4 DR. BADEN: Sure. I still am impressed with  
5 there's enough global need that you -- high quality  
6 data are out there to be had, in my view if I were  
7 a sponsor, because I see there are a lot of deaths.  
8 We can put that challenge on the sponsor to come up  
9 with a development plan that's convincing, but  
10 there's enough global substrate that one could  
11 imagine a development plan that could be, and  
12 sponsors are creative.

13 I'm sorry. Dr. Siberry?

14 DR. SIBERRY: We had some prior discussions  
15 about some 4 to 1 randomization in this step that  
16 confused me because my thought of this  
17 postmarketing is capturing information about use of  
18 the licensed drug in the real world. So I just  
19 wanted to confirm that this was not a plan for a  
20 randomized trial; that's one.

21 Then second, off-label use will absolutely  
22 happen. And if this is a tiny volume that people

1 like, and the bat nailed to the wall gets brought  
2 to the classroom, I'll bet you they'd much rather  
3 give that tiny volume to those 30 kids than the  
4 bigger volume.

5           So I think that our concern that a licensed  
6 product that's out there that has other  
7 characteristics that make it appealing won't get  
8 used may be a concern that's greater than reality.  
9 So I think the 6,000 good. We should be willing to  
10 count on information from global health settings,  
11 but I think, at least separately, we should also  
12 put a requirement to the sponsor of a minimum  
13 number of uses in the United States because I do  
14 think this is our opportunity to make sure we are  
15 collecting information about use in the United  
16 States.

17           DR. BADEN: But one could add to that that  
18 if it is approved and used, they can track use to  
19 infinity. There can be a higher resolution for an  
20 earlier number and a lower resolution, but again,  
21 250,000 were tracked elsewhere, and there were no  
22 failures. I'm not sure I believe it, but it was

1 believable enough to lead to approval.

2 DR. SIBERRY: The fact is any case of rabies  
3 in the U.S. is going to get attention, so we will  
4 absolutely have --

5 DR. BADEN: But Dr. Green told us about a  
6 case of rabies that we didn't know was rabies until  
7 18 months later when a transmission occurred. So  
8 I'm not sure --

9 MALE COMM MEMBER: [Inaudible - off mic]  
10 occurred at 18 months earlier.

11 DR. BADEN: No, but the person who died, we  
12 did not know was rabies. So there may well be  
13 rabies deaths that we don't know because it's a  
14 motor vehicle accident, and we're done.

15 Dr. Burgess?

16 CAPT BURGESS: I also had involvement in  
17 that case, and yes, the organ donor, the time from  
18 exposure to the donor's death was 18 months. And  
19 the time from organ receipt in the tragic  
20 transplant was ominously 18 months, and it was  
21 raccoon rabies, so that, yes, there are cryptogenic  
22 exposures and undiagnosed cases.

1 DR. BADEN: Dr. Follmann?

2 DR. FOLLMANN: This gets to the issue of the  
3 postmarketing studies randomized or not. And I  
4 guess the way it's written, it is agnostic on that  
5 point. But I had thought we definitely had  
6 discussed randomization, and that's like at a  
7 3 to 1 ratio, and I think that would be a preferred  
8 design to just looking at the 6,000.

9 I'm a little concerned about the risk,  
10 basically. We talked a lot about it; we don't know  
11 what kind of exposure there is, really; that's a  
12 big unknown. And having a control group here would  
13 help I guess deal with that unknown about are these  
14 really risky people are not.

15 For example, if we've got 6,000 people with  
16 head bites, would we really want to show 99.9  
17 survival as the bar? Maybe it would be lower.  
18 That survival rate is really tied to historical  
19 data, which defines risk in a certain way that I  
20 guess you could -- or defines exposure in a  
21 conventional way. That rate is tied to that  
22 definition of exposure, and I would have more

1       comfort if we had a control group in the  
2       postmarketing study.

3               DR. BADEN: Other burning comments on  
4       postmarketing? Dr. Siberry, you're signaling me.

5               So I will conclude our discussion there. I  
6       don't think it's a conclusive discussion. I think  
7       the issue in the postmarketing will have to be  
8       determined based upon the data for the package, and  
9       the product, and the other features. There are  
10       some arguments for postmarketing having a control  
11       group, which means a much more organized study.  
12       For some number to increase the data, that will  
13       have to be gauged based upon the product and the  
14       product characteristics.

15               There will be potentially off-label use and  
16       other types of use that will be many other streams  
17       of data, and I think additional studies may be  
18       targeted studies at key risk groups, be they  
19       immunocompromised, or pregnant, or pediatric, that  
20       one can target to gain either data in the  
21       non-exposed healthy individual or in the exposure  
22       setting, and that would also be an important

1 discussion with the applicant at the time the  
2 product was being moved forward and given its  
3 characteristics.

4           Whatever the study is, 6,000 with a  
5 comparator component, it will then be well beyond  
6 that, and that one would want to capture data at  
7 different levels of granularity each step of the  
8 way given the concerns raised.

9           I think we've had a very long and extensive  
10 discussion despite an extremely short and concise  
11 set of presentations. So I would like to, again,  
12 thank the agency for positioning such a robust  
13 discussion with the way in which the data and the  
14 questions were presented.

15           What I would like to do is to see, before we  
16 adjourn, if the agency has any comments.

17           DR. MURRAY: Well, the feedback was beyond  
18 our dreams. We didn't expect to get this much  
19 consensus and maybe certainly not a unanimous vote,  
20 and just a high-level agreement even on the  
21 nuances. So we're very thankful for that and  
22 almost surprised.

