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Center for Biologics Evaluation and Research

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P R O C E E D I N G S (8:30 a.m.)

Agenda Item: Opening Remarks/Introductions

DR. JACKSON: Good morning and welcome. I'm Brooks Jackson, the chair of the Blood Products Advisory Committee. I would like to welcome you to this session.

We have one topic today, to review this product of botulism antitoxin, heptavalent preparation by Cangene Corporation.

We would first like to do introductions. If you could introduce yourself, where you're from, what your expertise is in, I think that would be helpful.

DR. KUEHNERT: My name is Matt Kuehnert. I'm the director of the Office of Blood, Organ, and Other Tissue Safety at the Centers for Disease Control and Prevention in Atlanta. My expertise is in infectious diseases and epidemiology.

DR. GILCHER: Ron Gilcher. I'm the retired director of the Oklahoma Blood Institute in Oklahoma City and now do private hematology consulting. My expertise is in hematology and transfusion medicine.

DR. DURKALSKI: Hi. I'm Valerie Durkalski. I'm a faculty member at the Medical University of South Carolina. I'm a biostatistician and my focus is on clinical trials.

DR. DEMETRIADES: Good morning. I'm Demetriades.

I’m a professor of surgery and the director of trauma services at the University of Southern California, Los Angeles.

DR. KUZMA: Hi. I’m Jennifer Kuzma. I’m an associate professor of science and technology policy at the Humphrey School of Public Affairs at the University of Minnesota. My expertise is biochemistry, risk analysis, and oversight policy.

DR. MAGUIRE: I'm James Maguire, at Harvard Medical School. I’m an infectious disease specialist at Brigham and Women’s Hospital.

DR. STOWELL: I’m Christopher Stowell. I’m director of the Blood Transfusion Service at Mass General and also have an appointment in the Department of Pathology. My background is in transfusion medicine and clinical pathology.

DR. RHEE: My name is Peter Rhee. I’m a professor of surgery at the University of Arizona in Tucson. I’m a trauma surgeon. That’s about it.

DR. SCHEXNEIDER: I’m Katherine Schexneider. I’m at Walter Reed National Military Medical Center in Bethesda, Maryland. I'm a transfusion medicine consultant there, and my specialty is clinical transfusion medicine.

DR. BONILLA: I’m Francisco Bonilla. I’m an allergist/immunology at Boston Children’s Hospital and I

focus on immune deficiency and immunoglobulin therapy.

DR. SIMON: Good morning. I'm Toby Simon. I'm senior medical director at CSL Behring. My background is in transfusion medicine and plasma derivatives and donation.

DR. STEVENS: Good morning. I'm Ruth Stevens. I'm with Camargo Pharmaceutical Services. I'm chief scientific officer there. I'm a pharmacokineticist by training, clinical pharmacology, and interspecies scaling, modeling from animals to humans.

DR. ADLER: I'm Michael Adler. I work at the US Army Medical Research Institute of Chemical Defense. My team and I are working on botulinum toxin small-molecule therapeutics.

DR. SOBEL: I'm Jeremy Sobel. I'm a medical officer at the Centers for Disease Control and Prevention. For several years, I headed CDC's botulism clinical consultation service and botulism applied research program. My expertise is in epidemiology and public health.

MR. DUBIN: I'm Corey Dubin. I represent the Committee of Ten Thousand, after the 10,000 people with hemophilia who contracted HIV and HCV during the 1980s. And I represent A-PLUS, which is the American Plasma Users Coalition, at the table.

LCDR EMERY: Hi. My name is Bryan Emery. I'm

the designated federal official for this meeting.

DR. JACKSON: And I'm Brooks Jackson, the chair of pathology at Johns Hopkins University and a transfusion medicine specialist. My research is primarily in conducting clinical trials, Phase I, II, and III, for infectious diseases and includes immune globulin products as well.

Bryan is going to read the conflict-of-interest statement.

Agenda Item: Conflict-of-Interest Statement

LCDR EMERY: Good morning.

The Food and Drug Administration is convening the February 12, 2013 meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all participants of the committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict-of-interest laws and regulations. The following information on the status of this advisory committee's compliance with federal ethics and conflict-of-interest laws, including but not limited to 18 USC 208, is being provided to participants at this meeting and to the public.

FDA has determined that all members of this

advisory committee are in compliance with federal ethics and conflict-of-interest laws, under 18 USC 208. Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

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

At today's meeting, the committee will discuss and make recommendations on a biologics license application for botulism antitoxin, heptavalent A, B, C, E, F, G equine, sponsored by Cangene Corporation. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by members and consultants, no conflict-of-interest waivers were issued under 18 USC 208.

Dr. Toby Simon is serving as the industry representative, acting on behalf of all related industry. Dr. Simon is employed by CSL Behring in King of Prussia, Pennsylvania. Industry representatives are not special government employees and do not vote.

With regard to FDA's guest speakers, the agency has determined that the information provided is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments.

Dr. Stephen Arnon has an association with a firm that could be affected by the committee discussions.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest.

The conflict-of-interest statement will be available for review at the registration table.

We would like to remind members, consultants, and participants that if the discussions involve any other

products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with any firm, its products, and, if known, its direct competitors.

Thank you.

DR. JACKSON: Thank you, Bryan.

Our first speaker will be Dr. Robert Fisher, who will introduce the topic for today, including the questions for the committee.

Agenda Item: Topic I: Cangene's Biologics License Application for Botulism Antitoxin (Equine), Heptavalent, A, B, C, D, E, F, G

Introduction and Overview

DR. FISHER: Thank you very much. Good morning.

My name is Robert Fisher. I'm a staff fellow in the Laboratory of Plasma Derivatives in the Department of Hematology in the Office of Blood Research and Review, CBER, FDA.

Today we're going to be discussing a biologics license application received from Cangene Corporation for a botulism antitoxin, equine, heptavalent, A, B, C, D, E, F,

G. I will be interchangeably referring to this as botulism antitoxin and the product, for obvious reasons.

The product is hyperimmune product that's manufactured from equine plasma. It's a mixture of $F(ab')_2$ and Fab antibody fragments that binds all seven serotypes of botulinum neurotoxin. The indication being sought is for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A through G. This product is being reviewed under the Animal Rule, which was established for use when human clinical trials are not feasible or ethical.

The issue before the committee is that the agency is seeking the advice on whether or not studies performed under the 21 CFR 601 Subpart H Animal Rule regulations have provided reasonable evidence that botulism antitoxin, equine, heptavalent, A, B, C, D, E, F, G, has an acceptable safety profile and is likely to be effective in the patient populations for the indications being sought. These patient populations include adults and children.

A bit of background. Products coming to the agency are usually licensed based on studies performed in humans. This includes safety and efficacy trials. However, you can appreciate that for certain serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, nuclear,

or radiological agents, an alternative pathway is needed, because it would be unethical to expose volunteers to these substances. This indeed is why the Animal Rule was established. The agency does have experience products under these regulations. Six products have been approved using the Animal Rule. These were done at CDER.

The Animal Rule applies under certain conditions, typically when definitive human efficacy studies cannot be conducted because it would be unethical to expose human volunteers to a lethal or potentially life-threatening substance and/or field trials to study efficacy after accidental or hostile exposure have not been feasible for a number of reasons.

The regulations as stated in the 2002 final rule state that the FDA may grant marketing approval for a biological product based on adequate and well-controlled animal studies when the results of those animal studies establish that the biological product is reasonably likely to produce clinical benefit in humans.

There are certain conditions attached to this type of approval. The animal studies used to demonstrate efficacy must be adequate and well controlled. The mechanism of injury of the toxic chemical, biological, radiological, or nuclear substance should be reasonably well understood. Typically, more than one species ought to

be used to demonstrate efficacy of the product. The study endpoints in the animal studies should be based on survival or prevention of major morbidity. Finally, there should be pharmacokinetic or pharmacodynamic data in humans and animals that allows the determination of a dose that's likely to be effective in the human population.

There are certain caveats. The Animal Rule does not apply if alternative licensure pathways are available -- for example, if you can approve based on accelerated approval with human surrogate markers. The use of the Animal Rule does not preclude the requirement for human safety studies. The animal models merely substitute for human efficacy trials. Products approved under the Animal Rule are subject to additional postmarketing data collection on safety and efficacy. In addition, the agency may also restrict distribution of the product approved under the Animal Rule.

The agency has provided advice to industry in terms of how to comply with the Animal Rule. In 2009, a draft guidance was issued to provide guidance. This guidance identified key elements for the animal models used to demonstrate. This guidance has been revised based on input from industry and academia. It is hoped that the revised draft will be released later this year. Again, that's our hope.

I would like to point out that many of the Animal Rule products, or products considered under Animal Rule approval regulations, are suitable for fast-track designation. What this means is that there is a highly interactive review process in which the sponsor and the agency are in frequent communication, especially with regard to development and execution of the animal models. Also products may be reviewed under an accelerated timetable, as is the case with this product. We are reviewing this under a six-month review clock based on an unmet medical need.

The guidance identifies essential data elements that the applicant should address in their application to the agency. This includes:

• The characteristics of the pathogenic or toxic agent, including dosage, route of exposure, and mechanisms of pathogenesis.

• Host susceptibility, in terms of what the disease appears like in the animal and a comparison back to humans.

• This ties back into the natural history of disease. There should be data to demonstrate this.

• Triggers for intervention need to be defined, because animals can’t seek health-improving behavior like humans can. The animal studies need to be designed such

that the treatment trigger or the point at which the animals need to be treated can be related back to what actually happens in humans with signs or symptoms.

• The medical product actually needs to be characterized in terms of the dosage, the route of administration, et cetera.

In addition, there are specific animal model design considerations. Study endpoints, as I have mentioned, should be survival or prevention of major morbidity. The timing of the therapeutic intervention is critical. If you're seeking a postexposure prophylaxis indication, you need to treat the animals before symptoms appear. However, if you are seeking a treatment indication, you have to wait for symptoms to appear before you can treat the animals. That's the case with the product today. The route of administration of the therapeutic should be the same in the animal models as it is in the humans, and you should be able to scale the dose appropriately.

As I have pointed out, the agency does have some experience with using the Animal Rule regulations. To date, six products have been approved under the Animal Rule. I'll point out that five of these agents, the first five in the list, were initially approved using traditional methods. However, their indications were extended using

Animal Rule approval. The last one, raxibacumab, was approved in December 2012 for treatment of inhalational anthrax. This was licensed solely based on Animal Rule studies.

I would like the committee to keep these questions in mind as we're going through today's presentations. I apologize for the small type and lots of words, but I didn't have much of a choice in terms of fitting all this on a screen. I get a D- on creativity, I suppose.

Do the results from the efficacy studies of botulism antitoxin in guinea pigs and nonhuman primates, which are the two animal models that Cangene has used, provide sufficient evidence that the product is reasonably likely to provide clinical benefit for the treatment of humans with symptomatic botulism?

Do the results from safety studies in healthy human volunteers, efficacy studies in animal models, and clinical data from CDC's use of the antitoxin under IND support an acceptable risk-to-benefit profile for use of the antitoxin?

Do the animal studies and simulation modeling adequately support the proposed dosing in humans for adults and for children, for whom we have safety data, but we do not have any PK data?

Based on the limitations of the safety database in humans provided by Cangene and CDC, FDA intends to require a postmarketing study to monitor the safety of the antitoxin. We propose that Cangene utilize a registry to capture safety data on sporadic cases of botulism for a three-year period after licensure. Please comment on whether such a registry would be adequate to add to the safety data for use of the antitoxin in patients with botulism.

Some of the presentations will go into more detail about the registry. For now, just let me mention that the thought is, after this three-year registry, it would be placed on an inactive status until there was another botulism outbreak, which ties into question 5.

The Animal Rule requires postmarketing studies to monitor safety and efficacy of the products approved under the rule when such studies are ethical and feasible. To address this requirement, the agency proposes that Cangene reactivate the registry, as previously indicated, to capture safety and efficacy data in any mass casualty scenario. Please comment whether such a registry would be adequate to monitor the effectiveness of the recommended human dose in cases of botulism and to add to the safety data in humans.

Finally, please comment on the agency’s proposal

that Cangene should commit to a postmarket study to determine the blood levels of botulism antitoxin after therapeutic dosing in children in order to validate the dosing recommendations in the absence of a pediatric PK study.

Today's agenda will include presentations from some invited speakers, who will lay down some introductions, if you will, in terms of botulism and botulism antitoxin products. We'll start with Dr. Kovacs, with BARDA, the Biomedical Advanced Research and Development Authority, who will discuss the botulism medical countermeasure program. Dr. Arnon, from the Infant Botulism Treatment and Prevention Program at the California Department of Health, will describe human botulism and the causative agent, botulism neurotoxin. Dr. Rao, with CDC's Botulism Consultation Program, will describe CDC's experience with the antitoxin in human patients with botulism.

This will be followed up by sponsor presentations. We'll start with their chief scientific officer, with an introduction, followed up by Dr. Peterson, who will describe the unmet medical need for the product. Dr. Emanuel will present the non-clinical efficacy studies -- that is to say, the animal model data. Chris Sinclair will describe how this data can be used to

translate to a human dose. Finally, Dr. Babinchak will describe the experience with human safety, clinical experience with the antitoxin, and a benefit-risk analysis.

This will be followed by the FDA review presentations. I will present the agency's review of the animal efficacy studies. This will be followed up by Dr. Staschen, who will present a review of the clinical pharmacology package. Dr. Feuerstein will present a review of the clinical data in humans in support of safety. Finally, I will summarize the FDA reviews and present the questions back to the committee for their discussion and consideration.

That's it.

DR. JACKSON: Thank you, Dr. Fisher.

We're going to hold questions until 10:00. I think we'll have Dr. Kovacs come up and give the next presentation.

Agenda Item: HHS Botulism Medical Countermeasure

DR. KOVACS: Good morning. I would like to thank the chair of the committee, Dr. Jackson, and the FDA, in particular Drs. Fisher and Lieutenant Commander Emery, for the opportunity to present at this meeting. My name is Gerry Kovacs, and I serve as the director of the Chemical, Biological, Radiological, and Nuclear Medical Countermeasures Division at BARDA, the Biomedical Advanced

Research and Development Authority, in HHS.

Our mission at BARDA is to develop and provide medical countermeasures for CBRN threats, such as botulism, pandemic influenza, and emerging infectious diseases. We do this through public-private partnerships, with companies developing medical countermeasures that meet the required target product profiles specified in Health and Human Services requirements for these types of products.

Over the past decade, BARDA has been working with its sister agencies, CDC, FDA, NIH, and the DOD, to stockpile a cadre of medical countermeasures that could mitigate the negative health consequences of a CBRN attack.

As stated by Dr. Fisher, we cannot do the types of studies that we need to to test efficacy of these products, so we rely heavily on the Animal Rule. You'll hear more about the animal models that were developed by BARDA and Cangene to satisfy the Animal Rule.

I won't go through the six points for consideration that Dr. Fisher just went through. Suffice it to say that I look forward to a robust and productive discussion.

Before reviewing the data that will be presented by the sponsor and the FDA, we thought it would be important for the committee to understand the strategy that HHS has undertaken to prepare and respond to a botulinum

neurotoxin attack. Without delving into classified information or issues of national security, I will describe the threat, our medical countermeasure strategy, the requirements HHS has developed in terms of what types of medical countermeasures to develop and stockpile, our antitoxin procurement program, and the current clinical guidance developed by our colleagues at CDC on the use of these countermeasures in clinical settings, including naturally occurring cases of botulism.

Botulism is a neuroparalytic illness caused by potent toxins produced by *Clostridium botulinum* and other related *Clostridium* species. These proteins are among the most toxins known and exist in seven antigenically distinct serotypes, designated A through G. These toxins block the release of acetylcholine from synaptic vesicles at the neuromuscular junction, ultimately resulting in paralysis.

Botulinum neurotoxins have long been considered a threat. While these toxins are frequently associated with naturally occurring botulism due to foodborne outbreaks derived from improperly preserved foods, we also know that botulinum neurotoxins can be easily produced *in vitro* and, with the right technology, used as a weapon.

It is these attributes, including ease of production and high potency, that render botulinum neurotoxins a biological weapon threat and why the CDC

lists it, along with five other biothreats -- anthrax, plague, smallpox, tularemia, and viral hemorrhagic fevers -- as a category A threat agent. These are all agents that can be easily disseminated, result in high mortality, have the capacity to cause public panic and social disruption, and therefore require special attention from public health preparedness agencies such as ours.

Unlike many other biothreat agents, CDC also deals with a relatively constant number of naturally occurring cases of botulinum every year. My CDC colleague, Dr. Rao, will provide you with more information about these cases.

The estimated human lethal dose of botulinum neurotoxin serotype A is approximately 1 nanogram per kg. By comparison, the estimated human lethal dose of ricin is approximately 500 times that. To put this into real-world perspective, if the amount of sugar in that packet you see there was replaced with an equivalent amount of type A botulinum neurotoxin, that would be sufficiently to kill approximately 50 million people.

Because of their potency and other factors, botulinum neurotoxins have historically been pursued as biological warfare agents by multiple state-sponsored programs. At the time of the Gulf War, Iraq had produced large quantities of bot neurotoxin, some of which was

loaded onto military weapons. More recently, non-state entities have tried to use bot neurotoxin as a weapon as well. The Japanese cult Aum Shinrikyo attempted to use aerosolized botulinum toxin in Japanese cities on at least three occasions between 1990 and 1995. Fortunately, they failed. Finally, it has been reported that al Qaeda has attempted to purchase and use botulinum neurotoxin as a weapon.

Since the anthrax attacks of 2001, the US government launched a coordinated and very expensive effort to better prepare ourselves to respond to not only manmade threats, but also put in place infrastructure that will help us respond better to the forces of Mother Nature. In terms of botulism preparedness, the US has developed a two-pronged strategy that includes antitoxins, such as the product we're evaluating today, and the use of ventilators for those who have more advanced disease in which antitoxin may not be effective.

Botulinum antitoxin heptavalent is the drug we are considering today. It is an equine polyclonal antibody produced against all seven serotypes of bot neurotoxins. It's currently being stockpiled under the presumption that it may be used during a declared emergency under what's known as an emergency use authorization. The US government's intent has been and continues to be that all

medical countermeasures under development will be supported all the way through to FDA licensure.

The US government develops what are known as requirements for medical countermeasures through a multistep process that initiates at the Department of Homeland Security. A series of analyses of classified and unclassified data are used to generate the relative risks of different CBRN threat agents. Those that pose the highest risk are then run through a high-plausible-consequence scenario that takes into account parameters such as the probability of acquisition, the production capabilities, dissemination efficacy, and so forth. This analysis results in what is known as a material threat assessment, or an MTA, for a specific CBRN threat. An MTA predicts the number of potentially exposed people in such an event.

HHS then works with the Department of Homeland Security on public health consequence models. These models predict the potential number of people who would become ill, be hospitalized, and potentially die from the MTA scenario. This analysis helps inform public health officials about the types and quantities of medical countermeasures that would be needed for a specific threat.

In this case, the process of generating requirements for a botulinum neurotoxin exposure have been

completed a number of times, most recently in 2011. Based on this process, the US government determined that antitoxins were required against bot neurotoxin serotypes A through G and that the antitoxin could be a multivalent product, such as the one we're reviewing today, or a combination of products that covers the entire spectrum of the seven serotypes.

Today the current treatment requirement has been met with the bot product and HHS is working towards long-term sustainment of this important capability.

I mentioned earlier that many of the products we have stockpiled are not yet licensed. This slide depicts our overall strategy for having products ready for use prior to FDA approval. As products mature through the pipeline that you see there, we accrue essential safety and efficacy data on these products. At the point where you see there that pre-EUA filings are made, the CDC and BARDA file a pre-EUA dossier with the FDA on these products so that they may be used in the event of an emergency. This occurs, as you see there, somewhere between Phase II and Phase III trials, at a point where development of a correlate has been identified and sufficient animal efficacy data has been accrued.

The filing of the pre-EUA dossier triggers the stockpiling of the medical countermeasure, as you see

there. The medical countermeasure then is delivered to the Strategic National Stockpile, run by the Centers for Disease Control.

BARDA currently stockpiles one antitoxin. This product is currently in the Strategic National Stockpile, as I mentioned, and may be used in the event of an emergency. HHS has seen to it that the most rigorous animal models be developed to test this product for efficacy. This product also has been tested for safety and PK in normal healthy adults. It is important to note that BAT is the only drug product available to treat all seven serotypes of bot neurotoxin, and it is currently released by CDC for naturally occurring cases under their expanded access program.

Sometimes the drugs that we develop can be used for everyday public health incidents, as well as in a bioterrorist event, and thus serve to also fill an important public health need, as this one is. Since 2010, the CDC has used BAT for naturally occurring cases of non-infantile botulism.

This slide lays out for you how multiple agencies within the federal government work with the sponsor to make BAT available for public health use. Initially BARDA funded Cangene to develop the product BAT. Once sufficient data was collected for the use of BAT under an emergency

use authorization, BARDA began delivery of BAT to the CDC's Strategic National Stockpile.

The CDC is responsible for the storage and release of the drug. As we will hear about later, the CDC has a National Botulism Consultation Program in which they provide 24/7 clinical consultation and antitoxin release. They release BAT under their expanded access program and correspond with the treating physicians to collect clinical data associated with BAT use. This data is then shared with Cangene, the FDA, and with BARDA. You will be hearing more about this program later this morning from my colleague at CDC, Dr. Rao.

The current clinical guidance for suspected botulism is provided on the CDC website. Practitioners are encouraged to contact their state health department's emergency number if they suspect a patient has botulism. Based on historical data from previous licensed antitoxins and the data from the current expanded access program, it is believed that the earlier the diagnosis and treatment with antitoxin, the better the prognosis for the patient.

In closing, I hope I've been able to explain to you how the US government has generated a specific requirement for botulinum neurotoxin antitoxin based on a plausible-high-consequence scenario that estimates the number of intoxicated individuals and the types of medical

countermeasures needed to mitigate the health consequences of bot neurotoxin.

I'll close by restating our commitment at HHS to provide the safest and most effective medical countermeasures for the American people against botulinum neurotoxins and all other high-priority threat agents.

Thank you again.

DR. JACKSON: Thank you, Dr. Kovacs.

Next we'll have Dr. Arnon.

Agenda Item: Botulinum Toxin and Human Botulism

DR. ARNON: Thank you, and my thanks to the FDA for inviting me to be here today to share with you knowledge of botulinum toxin and the illness that it causes in humans, botulism.

Before I begin, because the ethics statement indicated that the agency determined on the basis of my submission of the conflict-of-interest form that I had a conflict of interest, I would like to explain to the members of the committee and to the audience what it consists of. I head the program in California for infant botulism. Our program produces the public service orphan drug, human botulism immune globulin. We distribute at cost for the approximately 100 patients with infant botulism in the United States each year. We contract with Cangene Corporation for the vial in my hand and for the

future lots, with its subsidiary Cangene bioPharma in Baltimore, simply for the freeze-drying and capping of the product.

That constitutes my sole relationship with this company. I would like everyone to know that. This is because Cangene is specified in the license application. Therefore, there is no discretion on the part of our program as to who we use to perform this service for us.

I'll just give this to the chair to circulate it to the other members of the committee.

Now to turn to our subject at hand. To speak about the toxin and the illness that it causes, my talk today will follow this order. If you'll forgive the formality, we will begin with a definition. I think everyone in the room is familiar with the illness and that it results from botulinum toxin. It is, of course, a disease of humans and other animals. The major producer of the toxin is *Clostridium botulinum*, but there are actually two other species that have acquired the capability of producing the neurotoxin, *Clostridium butyricum*, that produces a type E botulinum toxin, and *Clostridium baratii*, that produces type F. Both of these rare organisms were discovered because they caused infant botulism.

Clostridium botulinum is an obligately anaerobic spore-forming organism, shown here in colorized scanning

electron micrograph -- vegetative cells in the process of undergoing sporulation. You see the subterminal spores, which on Gram stain have the classic tennis racket appearance.

Turning to the toxin itself, it has the dubious distinction of being the most poisonous substance known. It is a simple dichain protein, two polypeptide chains joined by a single disulfide bond. We will see a picture of it in more detail in just a little bit. It is a toxic protein. It produces illness and death by flaccid paralysis, principally, because of its ability to cleave the so-called SNARE proteins, which, as we will see in a more detailed picture further on, are the mechanism by which synaptic vesicles are able to fuse with the terminal nerve membrane and release their neurotransmitters.

As has been already mentioned -- and, of course, as evident from the product under review today -- there are seven serotypes, arbitrarily assigned the alphabetical letters A through G. Four of them are known to have subtypes, but we won’t spend more time on that here today.

Importantly, the different toxin types are distinguished operationally. They are distinguished by the inability of an antitoxin raised against one toxin type to neutralize any of the other six toxin types. It is for this reason that a product such as we’re discussing today

needs to have neutralizing capability against all seven of the toxin types to be a comprehensive therapeutic and preventive product.

This picture is included to give an idea of what a mass casualty event involving botulinum toxin might look like. This is a naturally occurring foodborne outbreak that occurred in Finland some years ago. In the picture are approximately 300 silver foxes who died overnight from ingesting a contaminated feed. This is on just one farm in Finland. The product was distributed all over Finland to these fur farm foxes. That night 25,000 foxes died in Finland, and over the next couple of days, the total mortality rose to approximately 45,000. The outbreak was published, for those who are interested, by Dr. Lindstrom in *Applied Environmental Microbiology* a few years ago.

Now let’s turn to the molecule that has this capability. This is botulinum toxin. I would like to take you through the functional anatomy of the toxin very briefly, because it may come up in some of the committee discussions and other presentations.

Basically, as I mentioned, there are two polypeptide chains, one over here in red called the light chain, because it’s 50 kilodaltons in mass, and the other is the heavy chain, which is the rest of the molecule, in green, blue, and gold. You can see at the top heavy chain,

down here light chain. The light chain is the enzyme portion of the molecule. Botulinum toxin is a zinc protease. Its substrates, as we will see shortly, are the SNARE proteins.

Functionally, there are really three parts of the molecule:

• The enzymatic, also termed catalytic, domain, which is, of course, why it’s the poison.

• This, in green, is called the internalization domain. That’s what allows the enzyme to actually enter the cytosol.

• Then this combination of blue and gold is the binding domain, with the actual binding receptors here on the very terminal part of the molecule.

To turn to the basis of its toxicity, its mechanism, we have two slides here. The first is basically normal neuromuscular transmission. Botulinum toxin has the capability of interrupting all peripheral cholinergic synapses, but the most important one clinically is the neuromuscular junction. This is just a quick review of how it normally works. Here we have the nerve axon coming down and arborizing into the motor end-plates. That’s what this little square is. That’s the rest of the slide.

The signal comes down. Calcium enters the cell. The SNARE proteins, which are these guys here, fuse

together and bring the synaptic vesicle in apposition to the terminal membrane, with which it fuses and then releases acetylcholine into the synaptic cleft, where it joins with the receptors on the muscle cell to trigger muscle contraction.

With botulinum toxin poisoning, we have the following events. Here is the toxin binding, being internalized in an endosome into the cell. Then, through the chaperoning of the so-called internalization domain, the light chain is able to exit from the endosome. Then, depending upon the toxin type, it cleaves one or more of the particular SNARE proteins. Type C actually is the only botulinum toxin has the capability of cleaving two of the SNARE proteins. All the other toxin types cleave just one, but they do it at different sites along the substrate, as indicated here.

Once the SNARE proteins are cleaved, the synaptic vesicle is unable to fuse with the membrane. No acetylcholine is released, no muscle contraction occurs, and flaccid paralysis results.

We will now turn to the effects of the toxin and the clinical manifestations of this flaccid paralysis and how this leads ultimately, in the absence of effective treatment, to death.

There are five basic forms of human botulism.

They are listed here. Everyone has heard of foodborne botulism, through mother's admonitions not to eat from dented or swollen cans. But, in fact, through improvements in both commercial canning and home canning, and perhaps a diminution of home canning, foodborne botulism has actually become quite rare in the United States.

There is also infant botulism, recognized about 35 years ago, a different pathophysiology in which swallowed spores germinate in the large intestine of the infant and produce botulinum toxin from inside the body. This pathophysiology has also been recognized in adults, rarely.

Wound botulism is the analog of tetanus, in which botulinum spores are able to colonize, germinate, and multiply in a traumatized wound under anaerobic conditions and produce botulinum toxin in the wound.

There is inhalational botulism. The toxin can be aerosolized. It can be inhaled. There's one outbreak on record, occurring in the 1960s in an experimental laboratory in West Germany, where workers handling deceased experimental animals reaerosolized the toxin on their carcasses.

Inhalational botulism has been discussed in the context of possible bioterrorism, but it requires a certain amount of technical capability and sophistication that is

not necessary to use the toxin as a bioweapon. I don't think we need to go further with that now.

Iatrogenic botulism results from an overdose of therapeutic botulinum toxin. I think I actually went past that a little fast, but in addition, of course, to being the most poisonous poison, it has been a licensed therapeutic now for quite some time and is a wonder drug for many, many conditions, especially the dystonias and others, now licensed for conditions of broad prevalence, such as migraine, overactive bladder. It’s a very versatile molecule.

Turning to the illness itself, the basic features -- we covered some of these already -- as was emphasized by Dr. Kovacs, recognition is key. Dr. Sobel pointed this out in a review article also some years ago. It’s the high index of suspicion of the front-line physician that is essential to the recognition of either natural or intentional botulism. Unfortunately, because it is such an uncommon disease, many emergency room physicians and others really don't know what it is. We’ll see some evidence documenting that shortly.

What does it look like? This young man was chosen because he has very mild botulism. The textbook cases with fixed dilated pupils and so forth are easier to recognize. As I mentioned, it’s clinically a symmetric

descending flaccid paralysis. Here -- very mild -- he has droopy eyelids, ptosis. His gaze is slightly dysconjugate. He has flaccid facial expression, sort of a bored look. At the time these pictures were taken, he had type A toxin circulating just at the limits of detection by the mouse bioassay.

He was asked to give his maximum smile, and, remarkably, he can still do so. But notice the absence of smile creases up here around the eyes, the dysconjugate gaze still, the droopy eyelids.

This is infant botulism, showing the more extensive illness. The patient is unable to support his head. This is the nurse’s hand supporting it. You can see the marked ptosis, the flaccidity of facial and jaw musculature. It’s hard to appreciate from the photograph, but there’s generalized hypotonia in all the limb muscles as well.

How does all this happen? Very quickly going through the pathophysiology, I mentioned that it’s a descending symmetric paralysis, meaning it starts in the muscles of the head, face, neck, and then descends toward the feet, toward the hands. This is because of an anatomical arrangement. At the base of the brain are 12 so-called cranial nerves or bulbar nerves that innervate structures throughout the head, face, neck, and distantly

internal organs. But they come off the base of the brain, not off the spinal cord.

It happens that the blood flow to these structures, the muscles of the head, face, and neck, is really large relative to the muscle mass because of the need to supply the brain with a large blood flow. Here you have the carotid artery branch in to the internal and external, and then branches off these supply all these small muscles.

If we take a closer look at the muscles surrounding the pharynx, we see just how many there are and how closely they lie in juxtaposition to each other. Of course, none of us have to really think about what it takes to swallow. We just swallow. They are intricately and carefully coordinated through the brain stem.

Now when we look at them in further cross-section, you see those muscles you were just looking at are this thin little band here. Let me just orient you to some of the other structures in this. This is the tongue, this big bulb. This is the epiglottis. Here’s the beginning of the airway, the trachea. This is, in cross-section, the size of your airway.

When your tongue is paralyzed, when these pharyngeal muscles are paralyzed, and you can’t swallow your continuous oral secretions, and when these muscles

here in the back become flaccid and flop into the airway, you are unable to breathe. So death in botulism, unsupported, results from basically suffocation, airway obstruction.

This anatomy just highlights the need that was described earlier for a supply in the stockpile of the ventilators. It's very reassuring to hear the development efforts that are going on in this regard. Of course, with the ventilators is the need for the operators of those ventilators.

Having reviewed the pathophysiology of the illness, now let us turn to how it is treated.

The fundamental principles are meticulous supportive care and, as described, the need to attend to breathing and feeding needs, because the patient can do neither of these for himself. Specific measures, of course, are antitoxins. I wasn't intending to speak much about human botulism immune globulin until the conflict-of-interest statement was read. But now you have your little exemplary vial of it. Here we have, for the first time, a heptavalent botulinum antitoxin for human use, which is a substantial advance.

There has been one randomized, double-blind, controlled trial of antitoxin treatment in human botulism. This basically is because the disease is so rare, it's

impossible to design a clinical study otherwise, and also why the Animal Rule is necessary for evaluation of the present heptavalent antitoxin.

But in the clinical trial of human antitoxin in the treatment of infant botulism, antitoxin treatment was found to be very effective in relation to controls. It shortened hospital stay by almost a month. Most of that time came out of intensive-care time. It shortened ventilator time. It shortened time on feeding tube. It reduced hospital costs by approximately $100,000 per patient.

Now we turn to the adult circumstance and heptavalent antitoxin and its use as a possible therapeutic -- actually, any botulinum antitoxin. Clearly the identification of toxin in serum is an absolute indication for treatment with antitoxin because that’s the only way to remove the toxin therapeutically from the serum. Otherwise, the nerve endings will remove it from the serum and one will have illness.

The next set of slides summarizes data from the literature on the duration in which toxin has been detected in the serum of patients with botulism. As you look at these intervals, realize that the reason they are so long is because the possibility of botulism had not been considered up until that point by the attending physicians

and the patients had been managed with other diagnoses. A listing of the misdiagnosis of botulism is a very, very long list.

I will have a slide at the end that has all these references on it for you.

In this first study cited, almost a quarter of patients still had toxin in their serum more than two days after hospital admission. In the next one, approximately a third of foodborne botulism patients had detectable toxin in their serum and approximately one in eight of those positive sera was drawn more than three days after the food was eaten.

In one of the most remarkable outbreaks on record, an international outbreak from contaminated carrot juice, there were two patients in Canada who had been managed as Guillain-Barre syndrome, and only when the outbreak was recognized in the United States and publicized did people take the food history up north and then draw the sera and determine that these patients actually had botulism. This 25 days after onset of illness -- more than three weeks -- is truly remarkable for the presence of circulating botulinum toxin following a one-time exposure of eating the food -- in this case, drinking the carrot juice.

When we turn to wound botulism, we see that 50

percent of patients had toxin in their serum more than three days after onset of illness. The last reference is from a long time ago, but again more than a week after onset of illness, toxin was still detectable in serum.

So in summary, botulinum neurotoxin is the most poisonous substance known. The toxin is simultaneously a potential bioweapon threat, a versatile licensed therapeutic, and the cause of human and animal botulism. As we have seen, the illness itself is an acute, life-threatening paralytic disease. Pathophysiologically, all forms of botulism are a toxemia, and therefore it is very logical to treat them with an antitoxin administered intravenously.

The toxin can be found in serum for lengthy periods after ingestion of contaminated food. Hence, there is a relatively broad window of opportunity in which to administer antitoxin to therapeutic effect.

Now I'd be happy to take any questions. I guess we'll save them until a little later, after Dr. Rao.

There are the references. They're in your handout.

Once again, thank you very much.

DR. JACKSON: Thank you.

Dr. Rao.

Agenda Item: Experience with H-BAT Use in Humans

DR. RAO: Hello. Thank you for the invitation to speak here today. My name is Dr. Agam Rao. I'm the medical director of CDC's National Botulism Consultation Program. I'm here to speak with you about our experience with H-BAT in humans.

I would like to provide some background and start off by providing an introduction to CDC's role in botulism response. For over 45 years, CDC has provided public health emergency response for botulism. Through 24/7 clinical consultation and antitoxin release, we treat suspected cases quickly, perform surveillance for confirmed cases, and identify botulism outbreaks. Antitoxin has been provided for clinically suspicious cases in the US, suspected non-infant botulism -- that is, botulism in patients over 1 year of age -- and in infant botulism that is symptomatic and due to toxin type F.

You may wonder why CDC is involved in antitoxin release. CDC has a history of providing therapeutics for some illnesses of public health significance and has been the only source of equine-derived botulinum antitoxin in the US. Historically, there have been trivalent, bivalent, and monovalent antitoxins provided by CDC. Some have been licensed, while others have been investigational. Intracel H-BAT, A through G, was also provided in limited supply for

emergency use. Cangene's H-BAT, A through G, was first used for a symptomatic patient in January 2008. In March 2010, with the expiration of BAT A/B and E, Cangene's H-BAT became the only botulinum antitoxin provided by CDC.

BabyBIG, as Dr. Arnon mentioned, is the human-derived botulinum antitoxin licensed for infant botulism and is derived from plasma of persons immunized with pentavalent botulinum toxoid. H-BAT has been used in infants with symptomatic type F botulism.

H-BAT is available under a CDC-sponsored IND program because botulism is a serious and immediately life-threatening disease, there are no FDA approved alternatives, and H-BAT may provide therapeutic benefit. The collection of data through our treatment program has been deemed non-research by our IRB, is not a clinical trial, and evaluates safety but is inadequate for efficacy determination.

Before I explain the results of CDC's H-BAT clinical use data, I'd like to explain how we obtain this data. As I mentioned earlier, because botulism is a public health emergency, CDC immediately performs a clinical consultation for all suspected cases of botulism in the US, in non-infants. After consultation, if the case sounds clinically consistent with botulism, H-BAT, along with report forms, is sent to treating clinicians for those

cases. The report forms ask about several things, including adverse events, clinical status at discharge, discharge location, and the most likely diagnosis at discharge. These are all filled out by the treating physician according to that person's clinical judgment among other things.

We have had a very good success rate. We have been a 95 percent success rate in receiving much of this data, because we have been able to perform active data collection, sending reminder letters and phone calls at regular intervals reminding clinicians that this paperwork has to be returned to us. This active data collection has only happened during the time that H-BAT has been released by CDC.

We generally only evaluate adverse events that are serious and atypical. For adverse events that are not serious, we take at face value the clinician's report. A serious adverse event is an event that resulted in death, threat to life, or persistent and significant disability. An atypical event is one that has not been associated with previous antitoxins. We evaluate these by following up with the treating clinician and reviewing the medical record. Because we're in close contact with treating clinicians at the time of antitoxin consultation, as well as in the days following, through helping them answer

questions about antitoxin preparation and botulism in general, and assisting with the health department's investigation into all suspected botulism cases, we also receive anecdotal clinical experience verbally.

The laboratory testing that is done for any suspected cases of botulism is coordinated at the time of H-BAT release, but can take days. Testing occurs after H-BAT administration, since H-BAT release is dependent on the clinical characteristics. So while clinicians are concurrently working up other diseases on their differentials, lab testing for botulism is performed. Those results are reported back to CDC so that we know which cases are confirmed.

I'm now going to move on to the results of the clinical use data now. I'll present it in the order on this slide. I'm going to start off with the demographic information for H-BAT recipients and types of botulism that have been treated, and next discuss the adverse events and deaths that we evaluated for relatedness to H-BAT. After that, I'll mention some of the anecdotal clinical experience clinicians have given us and discuss CDC's experience with providing a second dose of H-BAT.

This graph illustrates the number of patients treated with Cangene's H-BAT during January 2008 to December 2012. On the x-axis is month and year of H-BAT

administration and on the y-axis is the number of patients treated. Two hundred thirty-one patients were treated during this time period. You can see that before H-BAT became the only botulinum antitoxin released by CDC, it was provided to four patients, all of whom had type F or were suspected to have type F botulism.

This is some demographic information about those 231 patients. You can see that male patients were treated more often than female patients. The median age was 46 years, with a range of 10 days to 88 years. All age groups and races were treated.

We have limited H-BAT experience with pediatric patients, though. Only 15 patients under 18 years have been treated, and only one of them was under 1 year. That happened to be the first H-BAT release that we did in 2008.

Caucasians were the most common racial group that was treated.

For more demographic information, the 231 patients treated resided in 34 states and the District of Columbia. H-BAT was also used to treat five patients in Mexico in October 2010, four, and then September 2011, there was an additional release.

This pie chart is restricted to laboratory-confirmed cases. As Dr. Arnon has mentioned and as I've mentioned earlier in this presentation, we release

antitoxin based on the clinical suspicion for botulism and laboratory confirmation is performer afterwards. So this pie chart is restricted to laboratory-confirmed cases and shows the breakdown of toxin types treated with H-BAT. All known naturally occurring toxin types -- that is, toxin types A, B, E, and F -- have been treated with H-BAT. Seventy-four percent of cases treated with H-BAT were toxin type A, which isn’t surprising because toxin type A is the most common toxin type.

This pie chart shows the breakdown of botulism transmission categories treated with H-BAT. Again this is restricted to laboratory-confirmed cases. Foodborne and wound botulism are the most common transmission categories in the US and account for 85 percent of treated categories our experience at CDC.

Moving on to the adverse events now, these are adverse events that are reported by clinicians. This table can be confusing, so just bear with me here. It depicts the percent and number of patients with and without a reported adverse event. On the far right, you can see that 87 percent of total patients had no reported adverse event. One or more adverse events were reported for the remaining 13 percent. But on our review at CDC of those adverse events, we found that some were not related to H-BAT. They were atypical adverse events that, once we reviewed the

charts, did not sound like they were related to H-BAT. They were things like decubitus ulcers or preexisting conditions like thrombocytopenia that were mistakenly reported as adverse events.

When we accounted for these incorrect reports, the percentage of adverse events related to H-BAT dropped to 10 percent of total patients, and that's what is reflected in the bottom right. The details of the adverse events and other important points from this slide are described in subsequent slides that I will present.

There were adverse events related to H-BAT in a total of 22 patients, 20 adults and two pediatric patients. Twenty-one of these patients had non-serious adverse events and one had a serious adverse event. I'll go into those in more detail.

The non-serious events are illustrated here. There were 34 adverse events reported in 21 patients for non-serious events. This table breaks down those 34 non-serious adverse events for adult and pediatric patients. You can see that fever and rash were the most commonly reported non-serious adverse events, comprising 26 percent and 15 percent of all non-serious adverse events, respectively. There are a number of other adverse events that are listed in this slide that occurred less frequently. In the footnote you can see ones that were

reported once.

I mention serum sickness here, because that has been associated with previous antitoxins. In fact, the physician reported mild serum sickness in one case, but upon chart review for that case, it appears that this may have been a soft call. The physician was hypervigilant to the thought of serum sickness occurring in the patient because of their consultation with CDC. Based on the chart review, it looks like the patient may only have had myalgias and that they resolved quickly on the day that the patient was transferred to another facility, some 12 days after antitoxin administration.

Only one patient experienced a serious adverse event. I'll go into some detail. This patient was a 10-year-old in Mexico who was part of a foodborne botulism outbreak there. The patient had been tachycardic before H-BAT administration. Then 1.5 hours after the infusion began, his heart rate rapidly dropped to asystole. The H-Bat infusion was stopped and the clinicians were able to successfully resuscitate him within five minutes. Then the H-BAT infusion was restarted. The patient was noted at the time of restarting antitoxin to be tachycardic, which they thought was due to the epinephrine that was administered during code. But then 30 minutes after restarting the infusion, the patient again became bradycardic to the 30s

to 40s, and H-BAT was completely stopped and not restarted.

The patient received a total of 70 percent of the pediatric H-BAT dose and recovered without sequelae. We were actually told that ten days after the serious adverse event occurred, he was even removed from mechanical ventilation and was interacting with everyone and seemed to be doing well. He did have a prolonged hospitalization of 60 days, but as far as we know, he recovered completely.

Our pediatric experience is shown here. As I mentioned earlier, we have had 15 patients treated with, a median age of 5 years, with a range of 10 days to 17 years. Seven boys have been treated and eight girls. The first H-BAT release that we did was for an infant, a 10-day-old infant. That’s the only infant who has been treated with H-BAT.

Noted here are the adverse events that we have seen in those 15 patients. In addition to the 10-year-old male I just described in detail for you, there was a 3-year-old male, who was febrile at 99.4 before the antitoxin was started and then his temperature went up to 101.8, and then resolved without sequelae. This was at a time when we were actually administering two doses of antitoxin to pediatric patients, based on a decision that was made with all involved parties -- FDA, Cangene, CDC.

I want to go into a little bit more detail about

the deaths that occurred. There were 11 deaths that were reported to us among H-BAT recipients. The first column is the age and sex of the 11 patients and then the second column shows the cause of death as determined by clinician report and also CDC's medical record review. Many of these patients had underlying medical problems that left them frail even before they got botulism and were severely affected by botulism. Many of them were mechanically ventilated. All patients seemed to actually tolerate the H-BAT infusion well. There were no adverse events during the infusion of the antitoxin. The deaths occurred at varying time intervals, between 8 hours and 175 days after H-BAT administration. There was no single cause noted.

As you can see from this table here, the deaths were varied. Hospital-acquired infections were common. As you can see for the first, the patient died from sepsis bacteria in the blood, possible endocarditis that was not pursued further because the family decided to not escalate care.

The second patient listed here had methacillin-resistant *Staph. aureus* pneumonia, ARDS. That was noted to be the cause of death, following patient septic shock and respiratory failure due to pneumonia.

The next patient, aspiration pneumonia, an 82-year-old. The outcome seemed poor, and so the family

decided to withdraw care.

There was a 27-year-old male who had multiple medical problems. He ended up coding some 27 hours or so after antitoxin was administered. The cause of that code was determined to be a mucous plug of his airway leading to cardiopulmonary arrest, and then he had devastating neurologic injury as a result. He had some herniation of his cerebellum. Care was withdrawn.

There was a 64-year-old who had respiratory failure from botulism and wasn’t going to recover from it and also had very extensive metastatic prostate cancer. The family withdrew care.

Respiratory care and complications from underlying medical problems, an additional 88-year-old patient, similar to the previous patient I just mentioned.

Myocardial infarction due to triple-vessel coronary artery disease eight days after antitoxin administration in a patient, again thought to be unrelated to antitoxin.

Then there were three unknown causes that I have mentioned here. The first is unknown because the patient had a very long hospital course and, during that hospital course, was intubated, had very serious illness, paralyzed. He ended up being discharged to home, and then one day after discharge, after that prolonged hospitalization, had

some vague complaints of just not feeling well and had a witnessed arrest. Because of the long period of time before EMTs were able to resuscitate the patient, the patient had an oxic brain injury. The cause of death was never really determined. There wasn’t an autopsy.

Next, a 64-year-old male, unknown because the patient had a very long hospital course, was known to have underlying respiratory problems, had been extubated recently, and then coded, unknown reasons why.

Finally, the last patient was a patient who was only treated at the hospital where we were in touch with the physicians for a very short time and soon afterwards was transferred to another hospital, where they spent the remaining 70 days. The death occurred at the other hospital. Unfortunately, we only can acquire the records from a hospital where the treating physician -- the patient signed consent to have those records sent. So we don't have any idea of how the patient died at the second facility.

From the medical record reviews, though, it does seem like the deaths may be unrelated.

Shown here is a scatterplot. Early H-BAT treatment may have an effect on outcomes in our experience. Timeliness of H-BAT treatments seems to be associated with duration of hospitalization. On the x-axis is the time

from botulism symptom onset to H-BAT treatment, in days. On the y-axis is the duration of hospitalization in days. The dots represent individual patients. The best-fit line is shown. There seems to be an association between early administration of H-BAT and fewer days in the hospital.

There are confounding issues, though, like toxin dose. You can see that there is some variability with early antitoxin administration. Some patients are severely affected and paralyzed very early on in their clinical course, which may account for the fact that antitoxin does not do much in the way of reducing their hospitalization.

This same information is confirmed in the anecdotal clinical information that we get from clinicians. Just as one example, we have had several outbreaks in the last two years from foodborne botulism. One of them was an outbreak in Utah in which eight cases presented with varying stages of clinical illness. Actually, in front of our eyes, while they were waiting for antitoxin to be delivered to them, they were progressing, and after antitoxin was given, there was no progression of symptoms.

Additional factors here as well, like toxin dose and host factors, may contribute, because some patients progressed faster than others.

Finally, I’d like to just say a little bit our experiences with a second dose of H-BAT. We have not

really released antitoxin twice for many patients. There have only been five patients who have received two doses of antitoxin. Two of those patients were pediatric patients who got the previously agreed-upon two doses of pediatrically dosed antitoxin, based on discussions with FDA, CDC, and Cangene. Those were two of the patients.

Another patient was one of the patients involved in the outbreak that I mentioned earlier in Mexico involving the 10-year-old boy. One additional vial of antitoxin was released for that outbreak because there was a suspicion that there was going to be an additional family member involved. That extra dose was used without CDC approval on one of the patients. That is considered a protocol deviation. That was another time that a second dose of antitoxin was administered, because the clinicians did not see an immediate response or reversal of symptoms. They were expecting antitoxin to be antidote.

Finally, the last two were actual second doses of antitoxin. They were new episodes of botulism in the same patient. The patients either partially or fully recovered from botulism and then were given another dose of antitoxin to treat a new episode of botulism.

We have over the last few months started retesting individual serum post-antitoxin administration to see if there is any residual toxin in people’s serum. We

have done this for 11 patients whose pre-antitoxin serum was positive. All of those have been negative. From a clinical standpoint, we haven't had any indication, other than the ones I've mentioned, for giving an additional dose of antitoxin.

There were limitations, though, of our program. H-BAT is provided under a non-research treatment protocol -- that is, it is not a clinical trial. It does not allow for formal assessment of efficacy. Adverse events were based on clinician report and taken at face value unless atypical adverse events or serious adverse events were recorded. The data is limited, with only 231 patients treated with H-BAT, and few pediatric patients. Despite our efforts for active data collection, some report forms were incomplete.

In conclusion, H-BAT treated 231 patients in multiple US states and Mexico. All botulism transmission categories and known types have been treated, but we have limited pediatric experience. Adverse events were reported in 10 percent of recipients, with fever and rash being the most common adverse events. There was only one serious adverse event, but this occurred in a pediatric patient. Anaphylaxis was not reported.

Deaths seem unlikely to be related to H-BAT, and early administration seems to be beneficial from a clinical

standpoint, as well as other data that we have.

I would like to thank the following people.

Agenda Item: Questions for Speakers

DR. JACKSON: Thank you very much.

If we could have the other two speakers come up, I think it would be helpful for the question-and-answer period.

Perhaps I can start off. Dr. Arnon, just in terms of some basic biology, in terms of the toxin itself, the different serotypes, what is the mechanism of the metabolism of these toxins or excretions just naturally, and their half-lives? Do you know?

DR. ARNON: As you might imagine, the opportunities to study that under natural conditions are somewhat limited. Basically, clearance through normal body catabolic processes -- i.e., uptake and degradation and what used to be called the RE system.

DR. JACKSON: But intracellularly, are those cells killed or is it metabolized and the cells eventually are restored?

DR. ARNON: I see. What happens when the toxin is in -- eventually, the toxin is degraded through the process inside the cell catabolism. But the duration of the light chain, the enzymatic portion, inside the cell is quite variable between the toxin types. For instance, one

of the reasons it is believed that the paralysis of type A toxins is particularly long and severe is because it is able to sort of hide inside the cell by partially inserting between the layers of the terminal cell membrane.

DR. JACKSON: Thank you.

Dr. Rao, a question for you. In terms of the H-BAT, it sounded like you stockpile this and it's at the CDC. In your study of 231 patients, you had to send it to them. So there was at least 24 hours between when you got the request, the report, and when it was received?

DR. RAO: Actually, the antitoxin is currently stored at a specific place by the Strategic National Stockpile, and then there are other sites, quarantine stations, around the country that have a certain number of vials. We're available 24/7. Those quarantine officers are available 24/7. When we have a suspected case, we call those quarantine stations. The one that's closest to where that patient lives immediately looks into flights and whatever else can be done. Sometimes state health departments will get involved to see if they can drive the antitoxin across various state borders. Fire departments help.

It's an immediate action. It's not 24 hours. Things happen quickly.

DR. JACKSON: But you would still many times have

to send it overnight or something like that, right?

DR. RAO: We try to get it around 12 hours or earlier. I don't have numbers, but --

DR. JACKSON: If it were licensed and presumably available, hospitals could have this as a --

DR. RAO: It will always be released by CDC. The current practices will --

DR. JACKSON: Okay, that will always be the case.

DR. RAO: Yes. Even with previously licensed antitoxins, this has been the way it has been.

DR. JACKSON: Is there a particular reason for this?

DR. RAO: CDC is involved in a lot of public health illnesses. This is one of them. There are a lot of antiparasitics that CDC releases. This is just another one of those.

DR. JACKSON: Timing is obviously very important.

DR. RAO: Right. It will still be us that’s doing the response.

DR. JACKSON: Toby.

DR. SIMON: Dr. Arnon, I know this is a little bit off the topic, but you introduced the immune globulin that you produce. Could you give us an idea of the balance between the use of that product versus the antitoxin that we’re considering today?

DR. ARNON: This really isn't fair to my CDC colleagues, because all of us distribute in relation to the recognized patients. As I may have mentioned, for the last 30 years, infant botulism has been the most common form of human botulism to occur in the United States. Typically there are about 80 to 100 patients recognized every year. Our human botulism immune globulin was licensed by FDA in October of 2003, so it has been in distribution for the past ten years or so. It has basically treated about 1,000 patients since licensure. It was distributed under treatment IND before that, between the conclusion of the randomized, controlled clinical trial in 1997 and licensure in 2003. So it has actually treated quite a few more than 1,000, but about 1,000 since licensure.

DR. SIMON: I see the products are given, one to infants and the other to the adults.

DR. ARNON: Yes. They are mutually exclusive populations, except for the rare instance when there is type F infant botulism caused by *Clostridium baratii*. The human immune globulin was obtained from plasma donated by botulinum toxoid-immunized volunteers. These are people who were immunized for occupational safety because they work in laboratories and handle cultures of *Clostridium botulinum* which are hot. The toxoid was a pentavalent toxoid. It's now withdrawn, after about a 40-year

lifespan, because it was no longer sufficiently immunogenic.

It consisted of toxoids against A, B, C, D, and E toxins. It does not have F toxin. Hence, when a baby gets infant botulism type F and it can be recognized early enough, then the call goes over to the heptavalent product. It’s actually been just an n of 1.

DR. DEMETRIADES: Dr. Arnon, you did the first and only randomized study. In the study you showed that treatment decreased hospital stay and ventilator days. Was there any effect on survival? What was the number of patients you treated? Can you tell us a little bit more?

DR. ARNON: Certainly. The study was published in *The New England Journal of Medicine* in February of 2006. You can find all the data there.

Basically, there was no effect on mortality because infants were not dying from infant botulism in the first place, even though it’s a severely paralytic disease. The fact that they were not dying is really a testimonial to the high quality of tertiary pediatric intensive care that is available in the United States. In other countries, the experience had not been so fortunate.

In terms of what the study showed -- oh, number of patients. We had 122 laboratory-confirmed patients, after the code was broken. Fifty-nine of those were

treated with human BIG, as we call it, and the others were the placebo group, and then comparing them. The primary outcome measure was length of hospital stay. We thought that was a very quantifiable and objective measure. The original entry criterion was that treatment had to be received within 72 hours of hospital admission -- so we treated within zero to three days -- because no knew how long after onset one can treat and still achieve efficacy. Of course, we were trying to show that it really made a difference.

So when treated within zero to three days of admission, treatment with what’s now BabyBIG shortened hospital stay by, on average, about 26 days, I think, per patient. It shortened the stay differently between type A patients and type B patients. Type A illness has the potential to be much more severe, as measured by length of hospital stay, than type B illness. But, on average, it shortened hospital stay by about a month, thereby saving approximately $100,000 per patient in avoided hospital stay. It shortened ventilator time by a couple weeks, tube feeding time by about ten weeks, and ICU time by, again, a couple of weeks. Most of the shortening came out of ICU time, because that’s where, in the absence of treatment, these critically ill, paralyzed babies had to be managed.

DR. EPSTEIN: A question for Dr. Rao. Can you

comment on the sensitivity of the assay for the neurotoxin and how that compares, for example, to a predictive lethal dose or a predictive respiratory paralytic dose?

DR. RAO: Actually, Dr. Arnon may be able to help with this. The mouse bioassay is the gold standard for detection of toxin. I'm sure there are cases that we don't recognize because too much time has elapsed and the toxin is no longer in the serum, and so it is not identified as a case. There is also probably very low --

DR. EPSTEIN: If you had an assay within 24 hours, what would be the analytical and clinical sensitivity of the assay?

I bring this up because we're talking about the possibility of a registry and being able to confirm a case and, in some way, quantitate an effect would be valuable.

DR. KOVACS: We can find out.

DR. EPSTEIN: While you're thinking, I have a question for Dr. Kovacs. Humans can be immunized with the toxoid. It's off-topic for today, but has there been consideration of an immunization strategy as a counterterrorism measure?

DR. KOVACS: Yes, there has been. The Department of Defense currently has a requirement for -- I can't remember which bot tox serotype vaccines they are working on right now --

DR. ADLER: It’s bivalent AB.

DR. KOVACS: As Dr. Arnon mentioned, that product has been used to immunize donors in a program for the product that he described earlier. The HHS civilian requirement does not include a vaccine.

DR. GILCHER: My question relates to what Dr. Epstein just asked, in this respect. And it’s to you, Dr. Arnon. In infants it’s primarily foodborne botulism, and we’re told by the pediatricians that honey is an absolute no-agent for a child under the age of 1. Yet, as we age, we no longer have that problem with honey. Do we acquire an immunologic resistance or is this a different kind of resistance?

That’s the first question.

The second question relates to all the people who are receiving Botox. Do they develop any kind of immunity, and could they be used as potential donors for an antitoxin? But do they then require an increased dose subsequently because they have neutralization antibodies when they are receiving the Botox?

DR. ARNON: Those are all excellent questions. I’ll try to answer them all.

In regard to the question of infant botulism, honey, and vehicles of spores, the important distinction between adult foodborne botulism and infant botulism is the

pathophysiology and the difference between ingestion of preformed toxin and the ingestion of spores in the absence of any toxin. In adult foodborne botulism -- well, older children and adults -- the spores have germinated, multiplied, and produced a toxin in the food, the spoiled food. When we eat that food, we are eating preformed toxin, together with the organisms. Therefore, in pathophysiological terms, it’s an intoxication, a food poisoning, literally.

In infant botulism the pathophysiology is different. It’s the spores that are really the cause of the illness through subsequent toxin production. The spores are swallowed and then trickle down the infant gut to the large intestine, where, rarely -- about 1 in 15,000 live births -- they are able to germinate, multiply, become vegetative cells, and produce botulinum toxin from inside the body, and the toxin is then absorbed.

The reason that honey is an unsafe food for babies, but not for the rest of us, is that honey has been an identified and known reservoir of botulism spores -- not toxin, but the spores -- for 30 years or more. Spores have been found in honeys from around the world by multiple laboratories around the world.

The reason we adults can eat honey and other spore-containing foods with impunity -- and your question

really gets at the heart of the pathophysiology of infant botulism -- is what's now called the microbiome, the intestinal flora. We adults, because we eat a diverse table food-type diet, feed our internal flora. They multiply. They diversify. We have a climax ecology. So when swallowed spores get down into the colon, they are unable to germinate, except rarely, in these few adult cases where there have been alterations to normal anatomy and normal physiology, and antibiotics to the flora, through surgery, inflammatory bowel disease, and antibiotics to change the flora.

So it's not an acquired -- well, starting about 1 year of age, it becomes acquired, because we develop a full climax intestinal ecology.

Now to your question about whether with therapeutic botulinum toxin administration, patients develop antibodies. The answer is, yes, in a small percentage, mostly from the larger-dose uses of the toxin for the large muscle conditions, the dystonias, cervical torticollis, things like that. No patients who have had it for cosmetic reasons, we have been told at our annual botulism research meeting, have developed antibodies. So that important material use still continues.

When a patient develops antibodies, they become resistant to further benefit of the toxin as a therapeutic

agent, but they do not develop high enough levels of antibodies to be useful to us in making our BabyBIG product. For that, we have to stimulate active immunity through use of the toxoid and then coordinate the plasma donation to immediately follow the boosting in order to get the anamnestic response and harvest that over the next eight to ten weeks.

DR. JACKSON: A couple quick questions, Dr. Rao. In your release of the antitoxin, they all got the one vial if they were adults. They all got the same dose, except for those that got two doses. Is that correct? You didn’t adjust for body weight or anything like that.

DR. RAO: No.

DR. JACKSON: Okay. The antitoxin -- is there any such product elsewhere in the world? We talked about the United States, but in Europe or anywhere, have they done trials? Do they have such a product?

DR. RAO: They have different products. They don't have Cangene’s H-BAT. They have other products.

DR. JACKSON: But they have clinical data or not?

DR. RAO: I don't think they have clinical data on them.

DR. JACKSON: But they do have a product.

DR. RAO: They do. I don't think they see as many cases as -- or they don't have as good a surveillance

system as we have.

DR. JACKSON: The other thing is, in terms of post-follow-up and postmarketing studies for a registry, in the material it sounded like these five clinical signs and symptoms are really the diagnostic thing you need -- a strong indication that it is botulism toxicity. But is that what you would be recommending for afterwards with the use of this product?

In the hospital we see patients come in with descending paralysis. They get plasmapheresed. We're not exactly sure what this is. I just wonder how effective we will be in terms of identifying these cases.

DR. RAO: We're always trying to get the message out that while you're working up other things -- like GBS, myasthenia, and other things that can be confused with botulism -- you contact us and we do a consultation with you and potentially administer antitoxin while you're waiting for other things to be worked up.

DR. JACKSON: But this assay you have sounds like it's an *in vivo* --

DR. RAO: Yes. It takes days.

DR. JACKSON: There is no --

DR. RAO: There's no rapid test.

DR. JACKSON: Not just a rapid test. There's no test to identify the actual protein, either through gas-

liquid chromatography or immunologic assay?

DR. RAO: There are a lot of things that people are working on, but there's nothing right now. Right now the clinical presentation is the cornerstone for treatment. That's supposed to be the trigger.

DR. JACKSON: Maybe we could ask the company later. Obviously they have developed an antibody to this toxin, and you would think you could have some assay that would label that and identify that relatively quickly.

DR. RAO: Time is still very important. Any test, unless it's a bedside test, is going to take time. We could get the antitoxin out there more quickly.

One thing about dosing, though, is that Cangene does have recommendations for pediatric dosing. One vial is always released by us. Then, depending on the weight of those patients, a portion of that vial is administered. But for people who are not pediatric patients, it's always just one vial, regardless.

DR. JACKSON: How long does the mouse bioassay take?

DR. RAO: It's variable. You can get a positive test result the very day that you start testing or it can take much longer than that. With inconclusive test results, it can take two weeks before someone is willing to stick their neck out and say it's positive.

DR. JACKSON: But you would still release it.

DR. RAO: We release antitoxin before any laboratory testing is done. We are coordinating the laboratory -- obtaining specimens, and we’ve already released the antitoxin.

DR. JACKSON: The use of this product, if approved, would still be -- it’s really up to the CDC to determine who gets it. Is that correct?

DR. RAO: That’s right. We’re the ones to do the clinical consultation with the clinicians and then we’re the ones to release antitoxin, depending on what we find from that consultation.

DR. JACKSON: Other questions?

DR. DEMETRIADES: Dr. Rao, in the view of 231 patients treated with antitoxin, the overall mortality was a little bit less than 5 percent. From historical controls, what is the mortality in patients treated only with support, mechanical ventilation, nothing else? Any idea?

DR. RAO: I don't have that information, but mechanical ventilation probably is doing a whole lot for saving people’s lives. Antitoxin is just halting the progression of illness and is probably improving certain outcomes, like the duration of hospitalization. But mechanical ventilation -- death, as Dr. Arnon mentioned, is

related to the respiratory issues. I can't give you a number.

DR. ARNON: Can I speak to that? Infant botulism was first recognized in 1976, and until the late 1990s, there was no other treatment for it except supportive care, meaning mechanical ventilation, feeding most often through tube, and careful positioning. We can save, at least based on the experience with infant botulism -- which, as we just described, has a different pathophysiology and is more of a sustained toxemia, potentially -- mortality was extremely low, in fact almost zero, in all those years pre-BabyBIG. As we were describing before, it's really a testimonial to the high quality of tertiary care in pediatric intensive care units.

But this low, almost-absent, mortality came at a price. The price was sometimes months and months on a ventilator. We tracked the length of hospital stays. I can tell you that the longest hospital stay in California in the pre-BabyBIG era was ten months, and in today's dollar, at a cost of over $1 million for this hospital care. Hospital stays of two, three, four, five months, with much of that time on a ventilator, were not uncommon.

These were infants. Why did they need to be ventilated so long? Because the nerve endings had to regenerate and there was nothing to neutralize the toxin

being continuously produced in the intestine and traveling through the circulation and picking off more neurons even as they tried to regenerate. So the net effect was these multi-month hospital stays.

Since availability of the antitoxin, the average hospital stay is two weeks and much shorter ventilator time.

Yes, you can sustain the patients on ventilators, but it will take months and months and months. This is true even in adults treated with antitoxin, because sometimes you don't get the antitoxin there soon enough to make a difference because of all these logistical considerations.

The other important difference in assessing this experience is the physiological difference between us adults and infants. We just think of infants as this little blob, this little organism, but basically a biochemical entity designed by nature to grow and proliferate. It’s got all these nerve growth factors. We think their nerve endings regenerate much faster than adult patients with botulism. There are reports in the literature of adult botulism patients who years later still can’t climb stairs or walk more than a couple of blocks. It seems like their nerve endings just never fully regenerate.

DR. SOBEL: For Dr. Kovacs or for any of you, in light of the comments about the effect of botulinum antitoxins in reducing the duration of paralysis -- you, Dr. Arnon, spoke about individuals, infants, and the reduction of ICU care needs from months to two weeks -- could you give us a perspective on what this might mean, not for the sporadic case of infant botulism or the small cluster of foodborne botulisms, but the kind of mass event that you and HHS are preparing for?

DR. KOVACS: As I said, without getting into too many classified data points here, all I can say is that the medical health consequence modeling that we have done is based on a foodborne attack that would intoxicate hundreds of thousands of people through a food that you probably all have had for breakfast this morning. Our intent is to have, as Dr. Rao said, product available to respond as quickly as possible.

In response to some of the questions related to diagnostics, BARDA is working currently with the CDC and others to develop a rapid diagnostic test that would allow us to respond much more quickly than the week or so that we have been discussing earlier, primarily to, of course, ameliorate the morbidity of intoxication.

DR. FISHER: I just want to briefly address the question about mortality. I found some historical data

from the CDC. Prior to the availability of antitoxins and supportive care, it looked like the mortality was in the 60 percent range. I can provide that reference if you're interested.

DR. SOBEL: May I make a quick comment? I think it's important to recognize that those data from CDC show that the breaking point between 60 percent mortality and 15, 10, 8 percent mortality occurred in the 1950s or so, at the point at which modern ICU care was just taking off and ventilator care was becoming known. Antitoxin was available, in this country at least, since the 1910s or 1920s. As has been said by Dr. Rao and by Dr. Arnon, it's very difficult to disentangle survival attribution between antitoxin and just good modern ICU care. Nevertheless, every one of us who has worked with antitoxin and botulism recognizes the notable clinical benefits of early antitoxin administration.

DR. JACKSON: We're going to take a 20-minute break. Then we'll come back and hear presentations from Cangene.

(Brief recess)

LCDR EMERY: I neglected to note the conflict-of-interest statement that Dr. Steven Pipe recused himself from the Cangene presentations and discussion.

DR. JACKSON: We're going to have about an hour

and 15 minutes of presentations from Cangene Corporation, starting with Laura Saward, who will be the first speaker. We're going to have the presentations and then we'll hopefully have about 15, 20 minutes for questions and answers.

Agenda Item: Cangene Presentations

Introduction

MS. SAWARD: Good morning. I am Laura Saward, chief scientific officer at Cangene, with overall responsibilities for the H-BAT program, a heptavalent equine-derived antitoxin for the treatment of botulism.

We thank you for the opportunity to present the overall data package of animal efficacy, translational efforts, and human safety and clinical experience that supports the positive benefit-risk profile for H-BAT.

As we've heard today, botulism is a life-threatening disease for which there are no available licensed products to treat both adult and pediatric patients over the age of 1. We are here to ask the committee's endorsement of the indication that you see here for the treatment of symptomatic botulism following documented or suspected exposure to botulism neurotoxin, serotypes A through G.

Historically botulism has been a fatal disease. If we look back to the 1950s, when mortality rates were as

high as 60 percent, when there was only basic supportive care and limited options for treatment. The data shown here from the CDC reported mortality rates for botulism over time demonstrates the potential added benefit of botulism antitoxins to the therapeutic options.

When the first licensed equine-derived botulism antitoxin for serotype A and B was readily available in the 1960s, we did see the overall mortality rates reduced by twofold or more. This was in combination with the added benefit of improving supportive care. However, the mortality for serotype E remained high, at around 40 percent.

In the 1970s, the antitoxin for serotype E was employed as a therapeutic option, and a similar decline in mortality rates for E was observed.

Over the subsequent decades, improvements in supportive care, as well as the education for early diagnosis of botulism, in addition to the use of antitoxins routinely, have contributed to the further decline in mortality rates to less than 10 percent. Over the past 60 years, equine-derived antitoxin therapy has become part of the standard of care and provides a much needed option to treat botulism by directly inhibiting the toxin and impacting the mortality of the disease.

The H-BAT development program led by Cangene

involves over 20 studies and is supported by the governmental agencies of CDC and BARDA. Our program leverages the historical Department of Defense program, which defined the dose for H-BAT. Following 9/11 and subsequent to the anthrax attacks, Cangene began working on the H-BAT program with the CDC to develop a broadly active, complete antitoxin that covered all seven known serotypes and was manufactured using a modern process. This product was intended to address the unmet need of a mass exposure or sporadic cases of botulism.

The initial program objective was to move towards an IND, with appropriate process development, assays, and controls, which was developed by late 2004. Subsequently the program funding was taken over by BARDA, which has provided critical technical and scientific support since 2006.

The first human experience with H-BAT occurred in a safety study in 2006, followed by shipments to the Strategic National Stockpile. Our first patient experience was in January 2008, when a 10-day-old infant with type F botulism was treated. This was the first of over 200 patients that have been treated with H-BAT over the past few years through the CDC expanded access program.

The last lot of the previously licensed equine antitoxin expired in 2010. From March 2010, H-BAT is now

the only antitoxin available for the civilian population. In 2011, H-BAT was granted orphan drug status.

H-BAT is made consistently and potently with modern technologies in a manner that maximizes the potential benefits, while minimizing the potential safety concerns. It’s a heptavalent equine-derived polyclonal antitoxin and has been manufactured using platforms similar to our FDA-approved products, WinRho, HepaGam, and VIGIV. The process begins with a collection of plasma by plasmapheresis from horses that have been immunized for one of the seven botulism serotypes. Plasma for each antitoxin serotype is then manufactured separately into bulk drug substances using our ion-exchange chromatography platform and then blended into the heptavalent product, which is filled into single-use vials that represent one dose for all seven serotypes.

Similar to human plasma-derived products, several key controls are in place to support the safety of H-BAT. First, at the donor level, the horses are vaccinated against a number of the common equine infectious agents. At the plasma level, each unit is screened for adventitious agents. The manufacturing process has incorporated several control steps for viral inactivation and removal, including the validated solvent detergent treatment and nanofiltration steps.

During the manufacturing process for H-BAT the Fc species-specific complementing fixing region of the antibody is removed by pepsin digestion to yield approximately 75 percent $F(ab)_2$ and 25 percent Fab antibody fragments. The intact monomeric IgG is reduced to undetectable levels at this step. The subsequent purification steps then remove the pepsin and Fc fragments, resulting in a consistent product with greater than 96 percent purity.

Potency of the product is measured by the neutralizing capacity *in vivo* using the validated, industry-accepted mouse neutralization assay.

Overall, the approach of Fc removal and product purification is taken to reduce the potential for hypersensitivity reactions. This is consistent with the broader class of equine-derived products with Fc removal that have been used successfully in humans as therapeutics for several decades.

The Animal Rule guidance from the FDA provides a path for approval when adequate and well-controlled human efficacy studies are not ethical or feasible, which is the case for botulism due to the sporadic nature of naturally occurring cases and the inability to study all seven serotypes in humans. We will present today that the H-BAT development program fulfills all criteria for licensure

under this rule.

Fulfilling the first element, there is a well-understood pathophysiological mechanism of the botulinum toxin which is consistent across all species. The mechanism of action of the antitoxin is simple and well characterized.

For the second element, the efficacy has been demonstrated in two animal species, guinea pigs and the rhesus macaque monkey. The disease in these models had the same progress and pathophysiology as has been seen in the humans.

For the third element, the animal studies' primary end point, survival, and the supporting secondary endpoints are clearly related to the desired benefits in humans.

For the fourth element of the Animal Rule, H-BAT's pharmacokinetics and pharmacodynamics were collected in animal and in human studies, which enabled the translation of the H-BAT response into the human setting. H-BAT has been shown to be well tolerated in two clinical studies involving normal healthy subjects and from the supportive information from the CDC on the expanded access program in botulism patients.

Our presentation will review the H-BAT development program and demonstrate how we meet each of the

elements of the Animal Rule and to address the unmet medical need and fulfill these regulatory obligations: the well-characterized animal models, therapeutic benefits, translation to humans, and clinical safety experience.

Let's now look at the rest of the agenda for the presentation. First, Dr. Gordon Peterson, a neurologist from Loma Linda University and one of our clinical investigators, will review the unmet medical need. Dr. Andrew Emanuel, the lead preclinical scientist for this program, will present the non-clinical model development and pivotal efficacy data, and describe how this data meets the expectations of the Animal Rule. Then Chris Sinclair, our vice president of strategic and operational planning, will discuss the translation of the non-clinical results to humans. Dr. Tim Babinchak, our global medical director and a practicing infectious disease physician, will present the human safety, clinical experience, and the assessment of the positive benefit-risk profile of H-BAT.

I'll now invite Dr. Peterson to present the unmet medical needs.

Agenda Item: Unmet Need

DR. PETERSON: Hello. My name is Gordon Peterson. I'm a neurologist at Loma Linda University in California and one of the clinical investigators of H-BAT's healthy volunteer studies, specifically using the model we

developed of localized, and therefore ethical, botulism in humans.

This schematic shows the normal neuromuscular junction, or synapse, where the nerve communicates with the muscle fiber. With the assistance of the SNARE proteins, synaptic vesicles, or packets of acetylcholine, fuse with the membrane and acetylcholine is released and depolarizes or activates the muscle fiber.

As we have heard, botulism is a rare but potentially fatal paralytic illness caused by botulinum neurotoxin, which is produced by *Clostridium botulinum* and other related species. These bacteria or their spores are very common, being found in dust and soil throughout the world. Once absorbed into the bloodstream, the toxin is spread throughout the body. One organisms produces one or more of the seven main serotypes of botulinum neurotoxin. Most cases of botulism are due to type A or B or, to a much lesser extent, type E, and a few human cases are due to type F, and rarely others. Very importantly, primates and humans are shown to be susceptible to all known types of botulinum neurotoxin.

All types of botulinum neurotoxin block the release of acetylcholine at the synapse and have a similar biological activity and a similar clinical effect, whether human or animal. Once inside the body, botulinum

neurotoxin is carried in the bloodstream to peripheral cholinergic synapses, where it binds irreversibly. Types A, C, and E cut SNAP25 at specific but different sites, while types B, D, F, and G cut VAMP. A defect in either of these critical proteins makes the SNARE complex inactive, with the result that acetylcholine vesicles cannot fuse with the membrane of the nerve terminal, and therefore acetylcholine cannot be released into the synapse. This lack of available acetylcholine leads to loss of function, paralysis of voluntary muscles, as well as autonomic nervous system failure.

The opportunity to intervene in the sequence occurs only before there is irreversible binding by the botulinum neurotoxin. Neutralizing antibodies such as those contained in Cangene’s H-BAT scavenge circulating toxins and prevent the toxin from binding to the synaptic complex.

Consistent with the mechanism of action, we have shown that H-BAT is capable of neutralizing botulinum neurotoxin in a pharmacodynamic study of 26 healthy humans. In this study a dose of H-BAT or placebo was administered intravenously to healthy volunteers. One day later, botulinum neurotoxin was injected into the extensor digitorum brevis muscle of the foot. As shown in this picture, nerve conduction studies were recorded from that

same muscle over 28 days after H-BAT infusion and compared with baseline to determine the effect on muscle function. Shown in red is the response to botulinum neurotoxin following infusion of placebo. There is an 80 percent loss of muscle function as defined by the amplitude of the nerve conduction study response. The response after H-BAT, shown in blue, shows no loss of muscle function over 28 days.

Similar findings were seen with botulinum neurotoxin type B and Cangene’s H-BAT.

The clinical presentation of botulism is usually symmetric cranial nerve palsies, such as eyelid ptosis, paralysis of eye movements, difficulty with swallowing and speech, as well as symmetric flaccid paralysis of voluntary muscles, often descending from the face to the limbs and, most importantly, affecting muscles of breathing, which may progress to ventilatory failure and death. There is often autonomic instability in addition.

Naturally occurring botulism occurs in several forms -- foodborne botulism, wound botulism, and now the most common, colonizing the gut in neonates and occasionally adults. With the increased use of botulinum neurotoxins for a variety of reasons, including cosmetic, and particularly to treat spasticity, iatrogenic botulism has occurred.

Botulism neurotoxins can also be aersolized and

can cause inhalational botulism.

Whatever the form of botulism, in all cases the absorbed botulinum neurotoxin enters the circulation and proceeds to the neuromuscular junction, where it binds and produces the same clinical signs and symptoms, and there is about the same interval from exposure to symptom onset.

Foodborne botulism is the classic form of botulism. I helped take care of an over-90-year-old lady with a fairly typical case. She ate borscht that she had made and bottled, and then was hospitalized a few hours later with chest pain, although later she said that the complaint of chest pain was just to get admitted to the hospital. Examination the next morning showed prominent eyelid ptosis and speech and swallowing problems. A diagnosis of botulism was suspected and bivalent antitoxin was given at 24 hours after ingestion and about 12 hours after the onset of any weakness. She still required intubation a few hours later, and a few days later, she was transferred, with ventilator, to a skilled nursing facility. She went home at four months and was back to living alone before one year.

Groups can also be affected. Let me give you one example. There was an outbreak of botulism in 209 attendees of a festival in Thailand in 2006, spread by contaminated locally canned pickled bamboo shoots. This

outbreak illustrates how readily even an unintentionally contaminated food can cause a large outbreak of botulism. What about a terrorist plot with contaminated food? There is no licensed product in the US to treat any of these people with foodborne botulism.

Let me tell you about a case of wound botulism. I was involved in the care of a 29-year-old man who was weak and intubated in the ICU. I had a working diagnosis of myasthenia or, less likely Guillain-Barre syndrome, since he had preserved muscle stretch reflexes and seemingly normal pupils. To help clarify the diagnosis, I did nerve conduction studies. Accidentally a subcutaneous abscess was popped during the nerve conduction studies. Then botulism was diagnosed and antitoxin given.

Later the patient admitted to skin popping, or injecting the drug under the skin, which is a typical mechanism in wound botulism, although abrasions can be the mechanism.

There is no licensed product in the US to treat wound botulism.

Although first recognized in the 1970s, today infant botulism is by far the most common form of botulism in the United States. The believed mechanism is by the infant swallowing spores, presumably from dust or some food, and the spores germinating in the gut. The resultant

bacteria produce toxin. The toxin is absorbed and results in varying degrees of poor suck, poor feeding, poor constipation, floppiness, weakness, paralysis, respiratory failure, and death if not supported and treated. Over the past 30 years, I personally have been involved in diagnosing at least a couple dozen of these infants by electromyogram and nerve conduction studies.

Currently BabyBIG is approved for babies under the age of 1 year with type A or type B botulism. There is no licensed antitoxin for children over the age of 1 or for infants for serotypes other than A or B.

In all cases of botulism there are similar clinical signs and symptoms. Botulism may be difficult to diagnose, since it is uncommon and since the early clinical signs and symptoms may be shared by other neurological diseases. The presence of tingling can usually be used to help identify Guillain-Barre syndrome, rather than botulism. The absence of pupillary dysfunction can often be useful in distinguishing myasthenia from botulism, but sometimes the pupillary abnormalities of botulism are subtle or even absent. Nerve conduction studies might definitively document features of demyelination seen with Guillain-Barre syndrome, and thus exclude botulism to explain the symptoms. Repetitive nerve stimulation can sometimes provide more support for a diagnosis of

myasthenia.

The confirmatory diagnosis of botulism is made via the mouse neutralization assay, which requires days to complete. This assay is performed on blood, stool, stomach contents, or especially a contaminated food source. The diagnosis often cannot be confirmed by this method. Importantly, though, there is no laboratory test that can rapidly identify the presence of botulinum neurotoxin or, if present, the serotype.

Let us turn to mortality and treatment. Certainly improved ICU care has helped greatly improve the prognosis, especially of ventilator-dependent patients, since the 1960s. But this data suggests that significant improvement seems also related to antitoxin. In the 1950s, mortality for botulism was about 50 percent. Equine-derived botulinum antitoxin for types A and B became more readily available in the 1960s. Along with better ICU care, antitoxin significant reduced the mortality for botulism caused by type A or B neurotoxin. However, mortality with type E neurotoxin remained essentially unchanged, until a type E antitoxin first became available in 1969. Thereafter, the mortality rate lowered for type E botulism.

We have talked about early diagnosis and administration of antitoxin and the better supportive care

of modern ICUs as treatment for botulism. In cases of intestinal botulism, we also try to remove unabsorbed toxin from the gastrointestinal tract with enemas. In cases of wound botulism, one would typically perform surgical debridement and irrigation of the wound and administer antibiotics.

The administration of antitoxin and the timing of that administration are both critical. Tackett et al. published the only case series to evaluate the efficacy of equine antitoxin therapy in type A foodborne botulism. They found that patients who received trivalent equine antitoxin had a lower mortality rate and a shorter hospital course and shorter duration of mechanical ventilation than those who did not receive antitoxin, and even shorter if treated in the first 24 hours.

In the 2006 Thailand outbreak that I mentioned earlier, 43 required mechanical ventilation. Some received botulinum antitoxin four days after exposure. The others received the antitoxin six days after ingestion. The early treatment group required mechanical ventilation for a significantly shorter duration than the later-treated group. There were no deaths in this outbreak in Thailand.

A study from Argentina of equine antitoxin in infant botulism also supports greater efficacy of early treatment.

Antitoxins were available for the past six decades. However, the last batch of bivalent antitoxin expired in 2010. Because of the inability to determine the toxin serotype at the time of diagnosis, ideally there would be one product that treats all seven serotypes of botulism in adults and in children -- a product such as Cangene’s H-BAT, which we are discussing today.

Now I will turn the presentation over to Andrew Emanuel.

Agenda Item: Non-Clinical Efficacy

MR. EMANUEL: Good morning. My name is Andrew Emanuel, and I’m the lead preclinical scientist for the H-BAT program. I will be presenting data on model characterization, as well as the data and conclusions from the two pivotal therapeutic efficacy animal studies which were performed in support of our proposed indication.

The Animal Rule states that efficacy of a product is required to be confirmed in more than one species. For this reason, well-controlled non-clinical studies were performed in the guinea pig and in the rhesus monkey. These two species are well-established models of botulism, having been extensively used in previous research. Both species are sensitive to all seven serotypes of botulism, and they exhibit clinical signs similar to humans -- progressive muscular weakness leading to respiratory

distress and paralysis, eventually resulting in death.

The efficacy of H-BAT was assessed against all seven serotypes in the guinea pig, while in the rhesus monkey the efficacy of H-BAT was confirmed with a representative serotype, serotype A.

The 20 studies that were performed as part of the non-clinical H-BAT program fall into one of four categories. The initial studies that were performed can be classified as model development and were completed in order to determine three critical aspects. Firstly, the clinical course of botulism was determined and the disease progression at various toxin doses assessed. Secondly, the early clinical signs of botulism that would trigger treatment with H-BAT were identified and characterized. Thirdly, the optimal toxin dose that would be high enough to ensure mortality of untreated animals, but would also allow a sufficient window for treatment with H-BAT was selected.

In addition, the use of supportive care was assessed in the rhesus monkey.

Pharmacokinetic studies were then performed to determine the profile of H-BAT in these two models, while dose-ranging studies assessed the efficacy of H-BAT when administered at a variety of doses to intoxicated but non-symptomatic animals.

Therapeutic model studies were then performed to refine the treatment of symptomatic animals with H-BAT and their results analyzed to ensure that therapeutic efficacy studies were appropriately powered.

As a result of all of these studies, the models used in both therapeutic efficacy studies were well characterized and predictive of the response in humans.

The signs and symptoms that characterized the disease in the two models were similar to those observed clinically in the human, although the clinical course, the speed at which the disease progressed, varies by species. In the guinea pig there’s an early onset of signs, specifically muscular weakness and respiratory distress, then a slow progression as these conditions worsen, eventually resulting in paralysis and death, although this time of progression does vary by serotype. In comparison, in the rhesus monkey there is a later onset, with muscular weakness, ptosis, or respiratory distress, but then a very rapid progression as these symptoms become more severe and result in death.

In humans the symptoms are similar to what is seen in the animals. Starting with bulbar palsies, progression to muscular weakness in arms and then legs, it leads within a couple of days to respiratory distress, followed by paralysis and death, if left untreated.

The toxin dose ensured that the disease progression in animals was reproducible, reliable, and comparable to that observed in humans. Consequently, any improvement in survival in animals would be relevant clinically.

I will now proceed and discuss the therapeutic efficacy study performed in the guinea pigs.

The objective of this study was to determine significant improvement in survival by serotype of H-BAT-treated animals over placebo controls. The primary endpoint was survival at 21 days. Key secondary endpoints included the time to death and incidence of severe signs. Although I will present results of the primary endpoint, survival, for all of the serotypes, due to the large amount of data generated, I will present detailed analysis of the secondary endpoints for serotype A only. The results of the remaining six serotypes are comparable and are presented in detail in the briefing book.

The pivotal therapeutic guinea pig study was randomized, blinded, and placebo-controlled. This schematic illustrates the study design for each of the seven serotypes. Guinea pigs are randomized to two groups, each group targeted to contain 17 animals per sex, for a total of 34 animals per group. Across all seven serotypes, a total of 476 animals were used.

The appropriate neurotoxin serotype was administered as a single intramuscular injection to the right hind limb of each animals. Animals were observed hourly, except in serotypes E and F, where observations were performed every 30 minutes due to the fast rate of clinical progression.

After the fourth consecutive observation of any predefined moderate clinical sign, animals were administered either a scaled human dose of H-BAT or placebo control. In the majority of animals, irrespective of serotype, these first four consecutive clinical signs that triggered treatment were right hind limb weakness. Survival was then measured at day 21.

This graph illustrates the improved survival of H-BAT over placebo-treated guinea pigs for each of the seven serotypes. Survival for H-BAT-treated animals, shown here in blue, ranged from 97 to 100 percent, compared to survival rates in the placebo groups, shown in red, of 0 to 50. All of the animals that died showed clinical signs consistent with botulism.

These results illustrate the significance of H-BAT, with a P value of less than .0001 for all seven serotypes. The conclusion from this analysis was that a single administration of H-BAT protected against a lethal toxin challenge of every toxin serotype.

This graph illustrates the difference in the survival rates over time between the two groups for serotype A. The H-BAT-treated group, shown here in blue, has 100 percent of animals surviving throughout the study. This compares to the placebo control animals, shown here in red, where, starting about three days postexposure, there is a relatively swift mortality, with the majority of animals dying over a period of two days, with the deaths of all remaining animals then occurring over the next four days.

This improvement in survival corresponds with a reduction in the severity and the delay in the progression of intoxication.

All animals, 100 percent of both treated and control, were observed with multiple moderate clinical signs -- specifically, the triggering clinical sign of right hind limb weakness and the additional clinical sign of change in breathing. Approximately 15 percent of treated animals subsequently progressed from these two clinical signs and developed weak limbs. However, no further progression occurred. The clinical signs of all treated animals eventually resolved, with animals becoming normal by study end on day 21.

In comparison, the clinical course progressed in placebo animals, with all animals developing weak limbs and

subsequently the severe sign of total paralysis. All placebo animals died or were euthanized.

Similar effects were observed in all species. In all cases treatment with H-BAT prevented the progression to severe signs, meaning that in these animals the disease is milder and less debilitating, which in turn allows the animals to recover and to survive.

The efficacy of H-BAT was clearly demonstrated in the guinea pig model. Individually, all serotypes showed a significant improvement in survival following treatment with H-BAT. This figure illustrates the overall efficacy for all seven serotypes, with survival rates in excess of 99 percent for treated animals compared to rates of only 13 percent among placebo controls.

In addition to this improved survival, treatment with H-BAT was also shown to reduce the severity of the disease, with a significant reduction in the incidence of severe clinical signs in all serotypes.

These results demonstrate the effectiveness of a single human-equivalent dose of H-BAT, which not only improves survival, but effectively halts the progression of the disease, preventing the onset of more severe signs of intoxication, irrespective of the specific intoxicating serotype.

I will now discuss the pivotal rhesus monkey

therapeutic efficacy study. The objective of this study was to demonstrate significant improvement in survival of H-BAT-treated animals over placebo controls. The primary endpoint was survival at 21 days. A key secondary endpoint was time to death.

The pivotal therapeutic efficacy study in the rhesus monkey was blinded, randomized, and placebo-controlled. This schematic illustrates the study design. Sixty animals, of which half are male and half are female, were randomized to two treatment groups and intoxicated intravenously with botulinum toxin serotype A. Each animal was observed hourly by a clinical veterinarian. At the onset of any predefined clinical sign of intoxication, animals were administered either a scaled human dose of H-BAT or placebo control. Immediately following treatment, all animals were provided nutritional supportive care and fluid support if needed, which continued until it was no longer required, based on each animal’s physical condition and dehydration state. Clinical observations continued until day 21.

Treatment with H-BAT resulted in an increase in survival of intoxicated animals, with 47 percent of treated animals surviving compared to 0 percent of placebo controls. This increase in survival was significant. All animals that died, both H-BAT and placebo controls, had

clinical signs consistent with botulism and were unremarkable under necropsy examination.

As presented earlier, the progression of botulism in rhesus monkeys is very rapid, with animals becoming symptomatic and requiring euthanasia in less than a day. This, combined with a clinical trigger occurring later in the disease course and the requirement for euthanasia of moribund animals, resulted in a short window for intervention with H-BAT. This shorter window for intervention resulted in loss of treatment benefits among 53 percent of H-BAT-treated animals. By the time these animals became symptomatic, a lethal dose of toxin was already bound at nerve terminals and could not be neutralized by H=BAT.

However, even in such a challenging model, a significant improvement in survival was seen with H-BAT treatment. It is anticipated that this would translate to a similar benefit in the human, given the slower, more protracted disease course observed clinically.

Among the H-BAT-treated animals, the time to death was prolonged compared to placebos. The median time to death was 190 hours in treated animals, compared to 75 in untreated. This means that although some H-BAT-treated animals do eventually succumb to the lethal toxin dose administered, they have an extension of the clinical

progression, including a reduction in the incidence of severe symptoms, which typically results in moribund animals being euthanized.

These results demonstrate the effectiveness of a single human-equivalent dose of H-BAT when administered to symptomatic animals. Treatment not only improves survival, but prevents the onset of more severe signs of intoxication.

The clinical efficacy of H-BAT has been demonstrated in two well-characterized models of botulinum intoxication and has shown that treatment with a scaled human dose of H-BAT results in a significant improvement in survival among animals administered a lethal toxin dose. In addition, treatment with H-BAT has shown clinically relevant beneficial effects on the disease progression, reducing the incidence of severe signs and delaying the time to death of intoxicated animals.

Now Dr. Sinclair will present the justification for the human dose.

Agenda Item: Translation to Human Dosing

DR. SINCLAIR: Thank you. I'm Chris Sinclair, vice president of strategic and operational planning at Cangene Corporation.

I'll now present the data that supports the human dose for H-BAT.

The next element of the Animal Rule is the translation of non-clinical results to humans. This incorporates the pharmacokinetic data from animals and humans, dose-ranging studies conducted in animals, and modeling and simulation work that we have conducted to bridge data from animals to humans.

The proposed one-vial adult H-BAT dose was initially based on historical information from previously developed equine botulinum antitoxin products. This provided the target potency levels, as well as the defined neutralizing capacity of the product relative to the known measured and anticipated human exposure levels of botulinum toxins. Cangene manufactured H-BAT based upon these specifications and subsequently confirmed the product’s efficacy and PK profile in dose-ranging studies in animals that demonstrated the ability of H-BAT to neutralize lethal toxin doses across a range of antitoxin dose levels, pharmacokinetic results from each of the three species demonstrating the similarity in the initial serum antitoxin concentrations and greater overall exposure seen in humans, and, finally, a modeling and simulation study which incorporated information from Cangene’s non-clinical and clinical development program.

While each of these pieces alone is suggestive, taken together they provide a multifaceted justification

for the H-BAT human dose.

The potency of H-BAT was initially established on antitoxin levels in other licensed and investigational botulism antitoxin products. Cangene manufactured the product to target the potency levels that were comparable to these previously available products. While the previously licensed products contain only antibody serotypes against serotypes A, B, and E, an investigational equine botulism antitoxin contained antitoxin levels against all seven known serotypes. H-BAT and these products had comparable levels with respect to antitoxin levels.

The target quantity for each serotype at the time of manufacture is greater than that, as shown here. The Cangene label claim, as described in this table, represents the lowest allowable potency over the proposed shelf-life of the product. This accounts for potential potency loss over time, as well as assay variability associated with the lethality model that’s used for determination of potency. This neutralizing capacity is in excess of the highest serum concentrations of toxin that have been reported in the literature for humans.

The second piece of the dose justification is the dose-ranging information from guinea pig and nonhuman primate studies. The objective of these studies was to

evaluate different doses of H-BAT in a lethal challenge model to confirm that adequate quantities of antitoxin are present in the proposed human dose. For both species, animals were randomized to placebo or H-BAT treatment groups and then they were exposed to a fixed amount of toxin. They were then treated at a fixed time point prior to the onset of clinical signs with an H-BAT dose less than or equivalent to the human H-BAT dose.

In the guinea pigs, we were able to do this for all seven serotypes at four different H-BAT dosing levels. However, in the rhesus monkeys, only serotype A and two doses of H-BAT were tested. The guinea pigs' and rhesus monkeys' survival was then monitored for 21 and 14 days, respectively. In the guinea pig dose-ranging study, there was an improvement in survival observed at all antitoxin dose levels for serotype A. There was a significant improvement in survival for the remaining six serotypes at dose levels equivalent to or greater than .2 times the H-BAT human dose.

Similarly, H-BAT enhanced the survival of rhesus monkeys even at the .1 times H-BAT human dose. There was a significant difference between H-BAT and placebo for both dosing levels tested.

These dose-ranging studies in the animal models provide evidence that the proposed human dose for H-BAT is

expected to be sufficiently large enough to neutralize a lethal challenge dose in humans.

The next piece of data supporting the H-BAT human dose is the noncompartmental pharmacokinetic results from each of the species that we tested. Here we see a snapshot of the pharmacokinetic parameters across species. For the sake of simplicity, only serotype A results are shown in this slide, as it is representative of the other six serotypes. These results demonstrate that the maximum concentration from a single human-equivalent dose is similar across species and that the overall exposure is substantially greater in humans. Thus, a human dose at the same level as was shown to be effective in animals will have a greater level of circulating antitoxin than was seen in the non-clinical program. This was true for all seven serotypes.

The last piece of information supporting the proposed human dose is the modeling and simulation study, which consisted of a population pharmacokinetic model and an exposure-response model. A population pharmacokinetic model was constructed to assess the pharmacokinetics of H-BAT from the three species used in the development program. The exposure-response was model was used to explore the relationship between H-BAT exposures predicted by the population PK analysis and the probability of survival

based upon dose-ranging studies.

Using the population PK model and data from the dose-ranging studies, logistic regression was used to explore the relationship between H-BAT exposure measures and the probability of survival following exposure to botulinum neurotoxins. The second column provides the overall exposure demonstrated in the noncompartmental analysis from the human pharmacokinetic study BT001. The third column is the predicted minimum efficacious exposure, which is the minimum exposure or area under the curve that is required to achieve greater than 90 percent survival, based upon the overall data set. For all serotypes, the actual area under the curve from the clinical PK study is higher than the predicted minimum efficacious exposure level.

As detailed in the fourth column, the probability of survival expected from the human-equivalent dose is expected to be greater than 93 percent, based on these results, which incorporates information from the overall development program. This is even in the absence of clinically relevant supportive care in the animal models.

Similar to the other elements of the dose-justification puzzle, these modeling and simulation results indicate that sufficient levels of antitoxin are present in the H-BAT human dose. Taken together, this provides

justification for a single H-BAT vial as the adult human dose. H-BAT is intended to be infused intravenously after a 1-in-10 dilution in normal saline.

Our proposed labeling also includes dosing recommendations for pediatric patients, including those under the age of 1. These pediatric recommendations are based on weight-based scaling techniques and prior product experience.

As was discussed by the CDC earlier this morning, there have been 15 pediatric patients that have been administered H-BAT, including the one neonate with type F botulism who was the first individual to receive H-BAT. The proposed pediatric dose is based on a pediatric scaling technique known as the Salisbury rule. For patients below 30 kilograms, they receive double their weight as a percentage of an adult dose, while those over 30 kilograms receive their body weight plus 30 percent. For example, a 20-kilogram patient would receive 40 percent of an adult dose, while a 40-kilogram patient would receive 70 percent of an adult dose. This an easy-to-calculate approach for pediatric patients that, as described in this figure, mirrors body surface area calculations. Published reports have indicated that pediatric dosing based on the Salisbury rule will minimize potential dosing errors.

Cangene is committed to confirming the benefit-

risk profile of the proposed pediatric dose through our postmarketing activities.

In summary, information from several areas has been used to support the proposed dose for H-BAT. The H-BAT potency is consistent with prior equine-derived botulinum antitoxin products that have been used clinically for more than 50 years. This provided the foundation for the H-BAT program.

H-BAT contains a broad neutralizing capacity that covers all seven known serotypes, and with levels expected to neutralize the highest level of toxin that has ever been reported in the literature. The scaled dose of H-BAT was efficacious in both guinea pig and rhesus monkey therapeutic efficacy studies, as was previously described. The pharmacokinetic data from the modeling and simulation studies indicate that there is a solid margin of efficacy. This is based on the measured serum antitoxin levels across species and the predicted antitoxin levels following a single dose of H-BAT.

H-BAT clinical experience demonstrates that the proposed human dose is well tolerated in healthy volunteers and patients with botulism and shows promising evidence of effectiveness in patients treated with H-BAT under the CDC’s expanded access program.

Overall, this provides confidence that the simple

one-vial H-BAT dosing regimen will provide benefit in adults with botulism, regardless of serotype.

With that, I will conclude the discussion of animal and translational efforts, and ask Dr. Babinchak to come and describe the safety and clinical experience with H-BAT.

Agenda Item: Human Safety, Clinical Experience, Benefit-Risk

DR. BABINCHAK: Good morning. I am Dr. Tim Babinchak.

I would like to present the human safety data that supports our conclusion that H-BAT has been characterized for safety and is well tolerated in humans. My presentation will cover human safety in normal healthy subjects and H-BAT-treated patients from the CDC's clinical experience.

The safety of H-BAT has been studied in the context of the known safety profile of the equine hyperimmune product class. Equine hyperimmune products have been used in humans worldwide to treat a variety of intoxications, including venomous bites and rabies. In addition to its applications as a medical countermeasure, H-BAT is intended to treat naturally occurring sporadic cases of botulism, replacing the previous equine antitoxins which have been part of the standard of care of botulism

for over 50 years.

The primary safety concerns for this product class are acute hypersensitivity reactions, ranging from mild anaphylactoid reactions to serious anaphylaxis, and delayed hypersensitivity reactions, such as serum sickness. The foundation for the rates of hypersensitivity reactions for botulism antitoxins was set by a CDC monitoring program in the 1970s. Looking at the CDC historical data published in 1984 by Black and Gunn with the previously licensed equine botulism antitoxin products, their case series found that 9 percent of the 286 patients experienced nonfatal hypersensitivity reactions, with 5.3 percent of those being acute and 3.7 percent delayed serum sickness. A subsequent report 12 years later, from Hibbs et al., with the use of heptavalent DOD antitoxin formulation, found similar rates of hypersensitivity reactions.

With this historical background in mind, Cangene conducted two clinical trials in 56 normal healthy subjects to examine the safety of H-BAT in humans. To supplement the clinical data, the CDC has also kindly provided information from their expanded access program. This program collected adverse drug reactions to provide a safety experience patient populations that may be exposed to botulinum toxins.

I will first discuss the safety information

collected for H-BAT in clinical trial, followed by information from the CDC’s expanded access program.

The first Cangene trial, BT001, was a single-center, double-blinded, randomized, parallel-arm study in which 40 subjects were administered either one or two vials of H-BAT. The primary objective of this study was to collect safety information and human PI data. The second trial, BT002, corresponds to the model study previously presented by Dr. Peterson and was also a double-blinded, randomized, parallel-arm study in which 16 subjects were administered a single vial of H-BAT and an additional 10 subjects received placebo. While the primary objective of this study was to examine the pharmacodynamic effects of H-BAT, this trial also provided valuable safety information.

The safety assessments conducted as part of these clinical trials included adverse events, vital signs, blood chemistry, hematology, urinalysis, ECG monitoring, skin sensitivity, and immunogenicity testing. Safety information from a total of 56 normal healthy subjects was collected during these clinical trials. The median age was 32 years. However, no pediatric or geriatric subjects were included in these studies of normal healthy subjects. The studies were gender-balanced. Thirty-six subjects were treated with one vial and 20 with a double dose of two vials of H-BAT.

In these Cangene healthy-subject trials, there were no deaths or SAEs reported. There were two subjects with AEs leading to discontinuation of the therapy. Both subjects had a moderate hypersensitivity reaction. Both of the subjects' skin sensitivity tests were negative and in both subjects anti-equine antibodies were not detected either before or after H-BAT administration.

The most common adverse events in subjects treated with H-BAT that occurred in more than 5 percent of subjects were headache and somnolence. Importantly, none of these AEs could be correlated to skin sensitivity testing or the presence of anti-equine antibodies.

These are the safety results of the double dose in 20 subjects in trial BT001 compared to the single-dose subjects. There was no difference in the number of adverse events and severity of adverse events between subjects receiving one or two vials.

I would like to now present the safety data from the CDC expanded access program, based on the information contained within our submission.

The purpose of this program is to enable the use of investigational H-BAT for treatment of individuals with botulinum toxin poisoning as a result of a naturally occurring outbreak or in cases of unintentional incidents. In addition, this program can provide safety information

across broader patient populations that was studied in the healthy-subject trials.

Between January of 2008 and December of 2011, 148 patients with suspected or confirmed botulism were treated with H-BAT. The patients ranged in age from 10 days to 88 years, with a mean of 46 years. During this time, seven patients 17 years of age or younger were treated with H-BAT, including five patients under the age of 6. In addition, 20 patients over the age of 65 were treated, including nine patients over 75 years. The majority of the patients were male, with only 29 percent being female. Most of the patients received a single dose of H-BAT. However, five patients received two separate doses, including three adult, one pediatric, and one infant patient.

From this program, six of the 148 patients died after receiving H-BAT. They were reviewed in the CDC program. Four patients were diagnosed with botulism, of which two patients died due to complications of their supportive care and two patients of unknown cause. The other two patients were diagnosed with other diseases and died of comorbid complications.

The CDC’s subject-matter experts, in consultation with the treating physician, determined that these deaths were unrelated to the administration of H-BAT.

Two of the 148 patients in this series experienced a serious adverse event. The first patient experienced an SAE of hemodynamic instability. The second patient had a cardiac arrest. The 10-year-old child who was part of a foodborne botulism outbreak, during the infusion of H-BAT, experienced bradycardia and asystole. That H-BAT administration was suspended and intravenous epinephrine was administered, and the patient recovered. After restart of the infusion, the patient experienced a second episode of bradycardia. H-BAT administration was suspended, IV epinephrine administered, and the patient's hemodynamic status again returned to normal. The patient received approximately 70 percent of the intended pediatric dose of H-BAT and recovered with no residual disability. As this instability may represent a positive rechallenge, it is currently reflected in our labeling.

The 27-year-old male was previously listed as one of the deaths. He had a complex medical history and a complicated hospital course before his H-BAT infusion. There were no observed adverse reactions during the infusion or immediately after completion of infusion, and the patient reportedly showed symptomatic improvement. Approximately one day after completion of the H-BAT infusion, the patient suffered a respiratory and then cardiac arrest. He was pulseless for 25 minutes before

circulation could be restored. The medical team believes that the cardiac arrest was due to hypoxia from a mucous plug during a procedure to change his tracheostomy tube. Because of the extensive neurological damage, the family made the decision to suspend supportive care.

The CDC's subject-matter experts, again in consultation with the treating physician, concluded that there was no evidence of an allergic reaction to H-BAT.

Other adverse reactions of potential clinical relevance reported included a male patient with mild serum sickness. The first patient was a 64-year-old male. He received one vial of H-BAT after his skin sensitivity testing was negative. After the infusion, he experienced mild diaphoresis that resolved within a few hours. The patient also had mild serum sickness, with myalgia, arthralgia, and dark urine 12 days after administration of H-BAT that resolved without specific therapy.

Eighteen patients receiving H-BAT reported adverse reactions following the administration of the product. The most common reactions reported by more than one patient included fever, chills, rash, edema, and nausea. In the case of pediatrics, a total of seven patients under the age of 18 were treated with H-BAT. Two of these patients had an adverse reaction. A 4-year-old patient with iatrogenic botulism had a temperature of 99.4

degrees Fahrenheit before administration of H-BAT. His temperature continued to be elevated throughout the administration of two doses of H-BAT 7 hours apart. The patient was treated with acetaminophen and recovered from the fever.

A second pediatric patient experienced the SAE of hemodynamic instability that I and the CDC have already discussed. There are no adverse reactions reported in the other five patients.

For geriatrics, a total of 20 patients over the age of 65 were treated with H-BAC. Only one of the 20 patients experienced an adverse reaction, which consisted of a localized rash.

In summary, Cangene studies in animals and humans provide a safety profile similar to other equine-derived antitoxin products. In our studies the experience with H-BAT does not provide evidence for an immunogenicity link to the hypersensitivity reaction, and no new safety signals were identified in either controlled clinical studies or the CDC expanded access experience.

In summary, Cangene believes that H-BAT has been demonstrated to be well tolerated in humans when administered at a dose of one or up to two vials to healthy subjects and when administered to patients with suspected or confirmed botulism.

I will now present the clinical experience data from the CDC expanded access program.

Clinically, as has been noted, mortality has declined over time due to both long-term supportive care and the ability of botulism antitoxin. In the animal program, where the use of mechanical ventilation is not possible, H-BAT treatment significantly reduced mortality and also reduced the duration and severity of clinical signs. In humans a reduction in the severity of clinical signs could be reflected by reduced durations of hospitalization, ICU care, and/or mechanical ventilation. The duration of hospitalization has been utilized as a clinically meaningful endpoint in previous analyses of botulinum antitoxins. Specifically, Tackett et al. demonstrated that the previously available antitoxins were effective at reducing hospitalization when administered soon after symptom onset. This may have the potential to lessen the burden on the medical infrastructure in the case of a mass exposure.

Although the CDC EAP was not designed to verify the efficacy of H-BAT, it allowed us to explore clinical outcomes, such as the duration of hospitalization in the intended patient population. The data collected was used to perform an exploratory post hoc analysis to determine whether H-BAT data was similar to that that was seen

historically.

The data in our BLA submission and that we will present here today include the 148 patients treated between January of 2008 and December of 2011. As a result, our data will not match the CDC presentation, which contained more up-to-date information.

Our exploratory analysis of clinical outcomes included 109 patients. This includes 99 patients with suspected or confirmed botulism, as well as 10 patients where the diagnosis was missing or unknown. We also evaluated a subset comprising 51 patients with a confirmed diagnosis of botulism or where botulism neurotoxin serotype was identified.

There were 39 patients who received H-BAT that had a different final diagnosis, such as Guillain-Barre syndrome or myasthenia. These patients were excluded from all summaries.

Given that early treatment with an antitoxin has been shown to be important in the treatment of botulism, we examined the time from onset of symptoms to treatment with H-BAT during the CDC expanded access program and found that the majority of cases were diagnosed and treated with H-BAT within approximately five days. It is anticipated that delayed treatment with H-BAT will have reduced efficacy, based on the mechanism of action. Therefore, we stratified

the data by early and late treatment, where early treatment is defined as within two days, to allow for the diagnosis and delivery of H-BAT, consistent with the clinical course. As expected with a heterogeneous patient population, we observed a large amount of variability, as evidenced by the standard deviation relative to the means. In both patient subsets, though, we observe a trend, with a shorter duration of hospitalization in the early treatment group compared to the later treatment group.

This data may provide a basis to guide future collection and study designs. Furthermore, these results are consistent with the mechanism of H-BAT, a product that binds free toxin in the circulation, and are supportive of the efficacy conclusions from the animal studies.

I would like to now present our benefit-risk assessment.

Botulism continues to carry a significant burden of morbidity and mortality even in its sporadic forms. The irreversible binding of neurotoxins at the neuromuscular junctions with the resulting blockage of acetylcholine release leads to the paralysis of voluntary muscles and symmetric descending flaccid paralysis. Involvement of the respiratory muscles leads to an inability to ventilate and, prior to modern mechanical ventilation, mortality rates of up to 60 percent.

While intensive supportive care has decreased the mortality, the weeks to months necessary for the reinnervation of paralyzed muscle fibers still results in prolonged hospitalizations, the need for mechanical ventilation, and significant morbidity.

As we heard from BARDA's presentation, the potency of the toxin and the ability for aerosolized delivery creates a heightened concern that botulism toxin may be used as a biological weapon. The resulting potential mass exposure might quickly stress or overwhelm that medical infrastructure.

Passive immunization with antitoxin is the only specific treatment available for botulism. As the only antitoxin for all seven serotypes currently available, H-BAT addresses the need for both a medical countermeasure and a therapeutic for naturally occurring sporadic cases. This unmet medical need can be addressed by H-BAT with the proposed indication: For the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A through G.

However, all potential therapies, even those indicated for life-threatening diseases, must be reviewed in light of a risk-benefit analysis.

For equine-derived antitoxin products, including the previously licensed botulism products, hypersensitivity

reactions were the most frequently reported adverse events. These have also been seen with the use of H-BAT, and the information is contained within our product labeling.

Because H-BAT is made from equine plasma, it may carry the risk of transmitting infectious agents. The equine plasma pools are screened for the presence of infectious agents and the manufacturing process for H-BAT includes measures to inactivate viruses and remove those.

Despite these measures, such products can still transmit disease. However, no cases of transmission of viral diseases have been associated with the use of H-BAT.

Since early intervention has been shown to lead to improved outcomes, there is also the risk that H-BAT will be given empirically to patients with neurologic signs and symptoms similar to botulism who are subsequently found to have other illnesses, such as Guillain-Barre syndrome. As we have heard, release of H-BAT will remain under the control of the CDC, in consultation with the requesting health-care provider, to limit this potential risk.

These risks must be evaluated in light of a disease that is debilitating and, if left untreated, can result in death. The previous study by Tackett et al. established the efficacy of an equine antitoxin for foodborne type A botulism, with a reduction in morbidity and mortality. The efficacy of H-BAT was clearly

demonstrated through the pivotal animal studies, with a significant reduction in mortality. Animal studies also demonstrated a reduction in the severity of the clinical signs of botulism, which could be reflected by reduced duration of hospitalization and other outcome measures in the clinical setting, as described in the literature and observed through the CDC expanded access program. The potential to reduce mechanical ventilation, ICU stay, and shorten the duration of hospitalization with a therapy specific to the pathogenesis of the disease could have important implications for the medical infrastructure in the event of a mass exposure.

Post-licensure, the CDC EAP will be discontinued and Cangene will perform a final analysis of the data collected. Going forward, the CDC will continue to control the release of H-BAT in the Strategic National Stockpile for civilian use and perform all standard surveillance activities, given that botulism remains a notifiable illness in the United States. Cangene has committed to sponsoring a patient registry to gather more data on H-BAT in the post-licensure setting. Details of the registry design are currently being discussed with the FDA as part of the review process and will be finalized in collaboration with all stakeholders, including the CDC.

This registry is being designed to verify the

safety profile and potential benefits of H-BAT used to treat patients with a confirmed or suspected diagnosis of botulism. It will be implemented as soon as possible after licensure and is intended to last at least three years, to ensure that data is collected across a broad range of exposure scenarios and patient populations, including pediatric and geriatric patients. A specific objective of this study will be the ongoing surveillance for potential adverse events, including hypersensitivity and allergic reactions.

The data from the CDC EAP will be used to identify appropriate outcome measures for the evaluation of clinical benefit, and an analysis plan for the registry will be prospectively defined.

Consistent with the Animal Rule, Cangene will launch a similar program in the event of a broad exposure scenario.

We have presented substantial and compelling evidence for the efficacy and tolerability of the heptavalent formulation of H-BAT that addresses all four elements of the Animal Rule. Specifically, H-BAT provides potent binding and neutralization to all seven types of botulinum neurotoxins that directly addresses the pathogenesis of the disease. The neutralizing capacity of H-BAT is demonstrated in two well-characterized animal

species, guinea pigs and rhesus monkeys, clearly showing a reduction in mortality. The reduction in the severity of botulism shown in the animal models is expected to correlate to the clinical situation as observed in the CDC expanded access program and in multiple publications.

The pharmacokinetic data and translational modeling results support an effective human dose of one vial. The pharmacokinetics in animals and humans showed a similar C_{max} in the higher rate you see in humans.

H-BAT has been well tolerated in healthy volunteers. The analysis of H-BAT use in the CDC program for the naturally occurring, isolated, unintentional incidents of botulism intoxication provides added confidence of the safety of H-BAT in the clinical population across age, gender, and comorbidities.

In addition, ongoing surveillance through an H-BAT patient registry is planned to verify the safety profile and potential clinical benefits in the post-licensure setting.

Therefore, all of these factors provide for a favorable benefit-risk profile for H-BAT. We believe that H-BAT should be approved under the Animal Rule.

On behalf of myself and my colleagues, I would like to thank the committee for the opportunity to present this data. I will now invite Chris Sinclair back.

DR. SINCLAIR: Thank you, Dr. Babinchak.

I want to briefly introduce the other subject-matter experts we have with us today, to answer your questions. We have with us today from Battelle Dr. Karen Gillum, who conducted the guinea pig program, from Lovelace, Dr. Denise O'Donnell, who was responsible for the rhesus monkey studies, from Pharsight, Dr. Martin Beliveau, who is the expert pharmacometrician on the modeling and simulation work.

In addition to Dr. Peterson, each of these external experts has been compensated for their expenses to be with us today.

We also have with us from Cangene Stephanie Sproule to address statistical questions, Derek Toth for any analytical or assay-related questions, and Dr. Christine Hall for specific clinical research-related questions. They'll be answering the questions from the back of the room.

With that, I thank you for your time. We look forward to addressing any questions that you have.

Agenda Item: Questions for Speakers

DR. JACKSON: Thank you very much.

We will open it up to questions now to the committee. Dr. Sobel.

DR. SOBEL: I have two questions. First, to

whoever on your panel would prefer to answer this, can you please explain the rationale behind testing only toxin type A in the monkey model?

DR. SINCLAIR: I'll ask Mr. Emanuel to come up to address that.

MR. EMANUEL: Toxin A was tested as a confirmation. Serotype A is the most prevalent serotype observed in the United States. It's the second-most prevalent serotype observed worldwide, and it has a more severe clinical course than observed with serotypes B or E, which are also observed frequently clinically. The efficacy of H-BAT was demonstrated against all serotypes in the guinea pig and confirmed against a single serotype in the monkey.

DR. SOBEL: In reporting survival data, as I understand from the report, that includes animals, guinea pigs and monkeys, that died, as well as animals that were euthanized. They are lumped together as non-survivors. Can you please explain the equivalence of a euthanized animal and an animal that dies of botulism?

DR. SINCLAIR: I'll ask Mr. Emanuel to come up and describe the techniques that were used for euthanasia.

MR. EMANUEL: The intention was to euthanize all animals before they died. Obviously, botulism being the disease that it is, with the death of the animals by

suffocation, we had criteria in place in both species that would require the euthanasia of these animals before they died. Once the moribund state of the animals was established, which was predefined prior to study start, for humane reasons, animals would be euthanized.

DR. SOBEL: Behind my question is, of course -- as reported, the assumption is that a euthanized animal was going to definitely. Can you assure us of that?

MR. EMANUEL: Yes. Based on the model development, studies that we had done, the criteria for euthanasia were built around, once they animals achieved that state, they were going to go. It was just for humane reasons stepping in and euthanizing them at that point.

DR. JACKSON: Other questions? Matt.

DR. KUEHNERT: I want to ask a little bit about the postmarketing surveillance. To me, this seems to be definitely a change and a bit of a challenge as far as the handoff, where the EAP is going to be discontinued and the company is going to do an analysis of adverse events. Are there going to be planned parameters of what you are going to be collecting concerning the adverse events? Are there going to be definitions on severity and imputability of the reaction in relationship to the product? How is that going to be coordinated between the company, CDC, and FDA concerning adverse events?

DR. SINCLAIR: I'll ask Dr. Hall to come up to discuss some of the specifics for the proposed program.

DR. HALL: First of all, we're very fortunate to have access to the CDC data from the expanded access program. We can use that to guide our efforts in looking for adverse events. We do have experience with another program where we're cooperating with the CDC and gathering postmarketing data. Typically what we would do in those programs is put together a protocol that would prospectively define criteria, such as how to define severity and how to assess relatedness to the product, that would first be assessed by the treating physician, but then could be reassessed by us as the sponsor.

What we have done in our other programs is -- the CDC, like they are doing now with their own expanded access program, provides all the documentation with the drug shipment. We would do the same. They would cooperate with us to notify us that the product went out, and we would be able to contact the treating physicians and their research units to help train them and know what we're looking for.

DR. SINCLAIR: And we are working with the agency and will be working with the CDC, ideally, in the postmarketing environment here to work out all the logistical elements and the handoff of that type of work.

DR. KUEHNERT: I'll maybe mention this a little

bit more in the afternoon. But I guess one concern I would have -- I guess what I'm asking is, the company would have the final determination, though, of whether it was associated with the product or not. Is that right?

DR. SINCLAIR: With standard pharmacovigilance reporting in the postmarketing environment, we would have a role in that, but in terms of the overall decision, we will report all information to the agency, in quarterly, biannual, or annual reports, as part of the vigilance databases that we submit.

DR. ADLER: In selection of doses, serotypes D and E are fairly close to the minimum and the others are 10- or 20-fold above. Can you give me the rationale for selecting those doses?

DR. SINCLAIR: Are you referring to the product or the toxin doses that were tested?

DR. ADLER: The product.

DR. SINCLAIR: The product itself was based historically on A, B, and E product, the licensed product and the investigational Department of Defense product. I'm sure you know it quite well. The levels themselves were based upon that historical information. The highest levels that you see from our product are the A, B, and E, which are the most common occurrences that we see in humans. In terms of the rationale, it was more of a historical

rationale.

DR. ADLER: Was there any difficulty in getting higher titers for those particular serotypes?

DR. SINCLAIR: I don't believe so, but I don't know.

DR. RHEE: I have a couple of quick questions on the modeling, just to clarify. I think you probably said this. After you dosed the toxin, then you gave the antitoxin. In the rhesus model, what was the interval between the toxin and the antitoxin?

DR. SINCLAIR: For the dose-ranging study, it was 4 hours.

DR. RHEE: It works better if you give it before they develop symptoms.

DR. SINCLAIR: That’s correct.

DR. RHEE: It was both 4 hours before the pivotal trial and the dosing trial as well. But it just so happened that one of them had a 50 percent survival and the other had a 100 percent survival.

DR. SINCLAIR: In the dose-ranging study that was conducted where the antitoxin was administered 4 hours after the toxin, we used 4 LD_{50} as the challenge dose. In the therapeutic study, it was 1.7 times the LD_{50}, and we administered the product approximately 50 to 60 hours after the toxin was administered, which once again demonstrates

the importance of time.

DR. RHEE: So it was 50 to 60 hours after the pivotal study.

DR. SINCLAIR: In the pivotal study, we administered the toxin at time zero and then approximately 50 to 60 hours afterwards. Once the animals were defined as being symptomatic, they would receive H-BAT.

DR. RHEE: Thank you.

DR. KUZMA: Given the lack of pediatric data, safety data or efficacy data, and the availability of the BabyBIG, could you summarize your arguments as to the unmet need and the risk-benefit ratio for kids?

DR. SINCLAIR: In terms of the unmet need, I can adders that. As Dr. Arnon described this morning, the product is licensed for the treatment of colonization in infants under the age of 1. For individuals that are not colonized, that have wound botulism or that have a foodborne botulism case in a pediatric individual, there is no available treatment for those patients.

In terms of the risk-benefit assessment, I'll ask Dr. Babinchak to come up and discuss --

DR. KUZMA: But for kids under 1 -- are you also looking for licensing for kids under 1 as well?

DR. SINCLAIR: We have proposed that. We do not intend to replace BabyBIG. It's in the cases where a

patient would have a serotype other than A or B, such as that type F. These are very infrequent. I believe fewer than 10 of the last 1,000 patients that have been reported in the US have had a serotype other than A or B.

DR. KUZMA: Then the risk-benefit ratio?

DR. SINCLAIR: I'll ask Dr. Babinchak to come up and discuss that.

DR. BABINCHAK: As Dr. Sinclair has said, this product is not intended to replace BabyBIG, the vast majority of the cases of infant botulism being A or B, but specifically has the potentially to be released upon identification or confirmation of a type F exposure.

As with every clinical situation, and especially in sporadic situations, the determination of the risk-benefit is going to depend upon the physician treating -- as we have heard for infant botulism, mortality is extraordinarily rare in that situation. However, morbidity, if left untreated, can still be significant. Therefore, the risk-benefit will have to be weighed by the treating physician at that time.

That being said, what we have seen through the development program and the CDC expanded access program is encouraging in that there is not an increase or any evidence of additional hypersensitivity reactions associated in the pediatric population -- given that the

infant population is an n of 1.

DR. KUZMA: Can I ask a follow-up to that?

DR. GOLDING: Can I comment regarding the children? If they are less than 1 year -- I think this discussion was about sporadic cases -- if we think about a massive exposure, I think it’s very different. There is BabyBIG available, but I think it’s rather limited. Dr. Arnon can say. But if there are thousands of cases involving very young children, less than 1 year, I would expect that we would consider using this product, if nothing else is available.

In that case, there would be an unmet need and we would consider this product.

DR. KUZMA: Is that because BabyBIG is less effective?

DR. GOLDING: It’s a question of availability. There’s a limited amount. As far as I know, the titers and the doses of BabyBIG are much smaller than what is contained in these vials. So it depends also on the exposure.

DR. KUZMA: I just think it’s important to have these more holistic discussions, because we are to consider unmet need and risk-benefit ratio. Thank you.

DR. ARNON: As the head of the program that developed, produces, and now distributes BabyBIG as a

licensed product, I would just like to briefly respond to these recent points. I recognize I'm not a member of the committee. But I think it's a very, very important point that has been raised here about a mass exposure. If the scenario is, as Dr. Kovacs has explained, through a common food vehicle, the fortunate thing about infants is that they have their own specialized diets. So hopefully a food vehicle that is consumed by the general population, including older children, would not expose infants, who are hopefully being fed their mother's breast milk or formula milk.

But to your immediate point, the supply of BabyBIG is very limited because it comes from human donors. Cangene has a great advantage over us of having a horse farm -- in fact, probably several horse farms. Horses are much, much larger. You can get much, much greater volumes. That's why there is a much greater supply of H-BAT than there is of BabyBIG.

DR. JACKSON: A question regarding the postmarketing. As I understand it from Dr. Rao's presentation and one of the others, it sounded like in the expanded CDC access program that fewer than half of the patients who got this product actually had documented botulinum poisoning or toxicity. You have a 12.6 percent adverse event rate, at least in one of the slide shows. In

fact, the majority of the patients who get this product will not actually have botulinum poisoning, at least if it's continued the way you're proposing. Is that correct -- unless you have a new test or something? Does the company have something that can better diagnose early this --

DR. SINCLAIR: No, we do not have a better test. We have used the mouse neutralization as the gold-standard method for both our non-clinical program, the development program on the clinical side, as well as the product testing.

In terms of the specifics surrounding the tolerability of the product in patients that have confirmed botulism versus those that don't, I'll ask Dr. Babinchak to come up and describe the results.

Before he does, though, I will mention that -- and I don't know the CDC data presented this morning that well -- those were confirmed cases. There were still also suspected cases that did not have another diagnosis.

DR. JACKSON: But I think your neurologist, Dr. Peterson, mentioned in his presentation that there were a significant number who were found later to have had other causes for their neurologic --

DR. SINCLAIR: I think there was a working suspicion in the case that he described, where the patient

had not received antitoxin because there was a suspicion of myasthenia or Guillain-Barre. But subsequently it was determined, based on the abscess.

I'll ask Dr. Babinchak to describe the data between botulism versus non-botulism patients treated with H-BAT.

DR. BABINCHAK: With regard to the specific question concerning those individuals that had a final diagnosis other than botulism, in the data set going up through 2011, the information is provided on the screen, where approximately one-third of the individuals were diagnosed as not having botulism. In the safety summary that you see there, the number of adverse reactions and the types of adverse reactions that were seen were similar between those individuals with botulism and those individuals without. Most were a difference of one patient between the groups.

DR. RAO: The adverse events and deaths that were reported in my presentation were for all patients, not just the ones that had confirmed botulism. We have continued to release antitoxin with low threshold just because we think the clinical benefits outweigh the risks and we've seen such mild adverse events with the H-BAT that we have released in the last three years.

DR. JACKSON: Well, then does CDC or BARDA have a

rapid test that can --

DR. RAO: No. I know there’s a committee at CDC. There’s a group of us, a workgroup that is always working on this, to try to figure out if there’s a better way to diagnose botulism so that we can limit the antitoxin releases. But there’s really nothing on the horizon for a rapid test right now. I know there are a lot of people working on it and there’s a workgroup within CDC where we’re always discussing the different tests. But right now it’s really about the mouse bioassay and mass spec, eventually, too. Mass spec is being used right now.

DR. JACKSON: Because clearly the timing is very important. Given prophylactically, it was virtually 100 percent protective. Getting an early diagnosis is clearly extremely important here. You want effectiveness, not just efficacy.

DR. STEVENS: I also would like to address some of the postmarketing -- there was modeling done in adults. In terms of predicting for pediatrics, you would like to use the Salisbury method. Could anybody talk about that modeling and this pediatric dosing that is suggested? It looks like the safety is fine, but how will you determine efficacy? Is there any postmarketing data that will be collected in terms of efficacy for the right dose?

DR. SINCLAIR: We will include information in our

registry from all patients that are treated in the postmarketing environment, so there would be pediatric patients enrolled in the study. Outcomes would be one of the pieces that we would be looking at to confirm that this dose that we propose based on the Salisbury rule will be effective as well as safe. I believe one of the questions that you will be discussing this afternoon surrounds additional pediatric elements in the postmarketing environment.

DR. STEVENS: Just a lot of the modeling was done on exposure, which is area under the curve. Are any blood samples being planned to take, because that’s what predicted survivability?

DR. SINCLAIR: I believe question number 6 deals with the possibility of doing additional blood tests. As the CDC described this morning, they have just started doing some post-dosing testing of patients that have received H-BAT.

DR. STEVENS: Including pediatrics.

DR. SINCLAIR: I don't know if there are any pediatric patients enrolled.

DR. DEMETRIADES: In the experimental study, the time from administration of the toxin to antitoxin was, on average, about 4 hours.

DR. SINCLAIR: That was in the postexposure dose-

ranging study. In the therapeutic study in the nonhuman primates, it was closer to 60 hours.

DR. DEMETRIADES: In the clinical situation, this time will be maybe one or two days. Are you planning any further experimental studies to see if it will work 24 hours, 48 hours later?

DR. SINCLAIR: At this point in time we are not. The absence of clinically relevant supportive care in the animal models would suggest that it’s unlikely to be as beneficial at a later time point.

DR. ADLER: This is addressed to Dr. Peterson. In the human study the antitoxin was administered 24 hours before toxin, whereas in all the other studies it was administered after onset of signs or at a fixed time point afterwards. What was the rationale for pretreating with the antitoxin in those experiments?

DR. SINCLAIR: The rationale was associated with the mechanism of action. Because it is administered locally, the toxin, the goal was to have the antitoxin distribute into the muscle such that it could bind the toxin at the time of administration. We don't believe that if we were to do a later time point, such as at the same time as Botox or Myobloc or after, this would really affect the determination of whether H-BAT would be efficacious or not. Consistent with the mechanism of action, you would

expect that this toxin would be taken up by the nerve terminal very rapidly and antitoxin would not be able to reverse the symptoms from the use of Botox or Myobloc. It's the EDB model. It's not symptoms. It is the electrical signals that would be detected.

DR. ADLER: Were any studies done to confirm that in the humans?

DR. SINCLAIR: We have not performed any studies of that nature.

DR. KUZMA: I'd like to go back to the adverse reports data. How does that compare to the older version of BAT, the ABE one? What is the percentage of adverse events for that particular product, which we've used for a decade or so? I forget exactly how long.

DR. SINCLAIR: It's very similar. I'll ask Dr. Babinchak. It was in his core presentation. The slide from Black and Gunn and Hibbs describes the previous experience.

DR. BABINCHAK: What I've provided here are the previous BATs. The first column is the Black and Gunn data that looked at the previous ABE product. The next column is a report of the use of a DOD product in an outbreak in 1996.

If I can have my last core slide, please, I can superimpose the data for H-BAT from the 146 patients in our

database from the CDC expanded access program through 2011.

Importantly, in this situation, the additional patients that have been reported do not change these numbers.

DR. KUZMA: That’s just hypersensitivity, though. Do you have any adverse reaction in a different slide that has 12.3 percent? Do we have comparative data for that?

DR. BABINCHAK: As the previous studies were taken from the literature, we don't have that level of detail to present.

DR. KUZMA: Thank you.

DR. DEMETRIADES: In the clinical scenario, if the diagnosis is made four, five days after symptoms, would you still recommend administration of the BAT?

DR. SINCLAIR: I think as Dr. Arnon described this morning, there is a wide potential treatment window where the botulism antitoxin would be expected to be beneficial. In the majority of the CDC cases that were presented this morning and in our data set, the vast majority were treated within five days. So, yes, we would recommend that.

DR. JACKSON: Okay, if there are no more questions, we’ll take an hour break for lunch and resume with the FDA presentations.

(Recess for lunch)

AFTERNOON SESSION

Agenda Item: FDA Review Presentations

DR. JACKSON: We have four presentations from the FDA, four speakers. We're going to start with Dr. Fisher again, who will be the first speaker, on review of animal efficacy studies.

Agenda Item: Review of Animal Efficacy Studies

DR. FISHER: Thank you very much, Dr. Jackson.

It seems I was just here a few minutes ago. I guess I have the dubious honor of welcoming everybody back from lunch. Hopefully I can keep you awake for the next 20 minutes or so.

What I'm going to do is present the results of the FDA review of the material that was provided to us by Cangene in their biologics license application for botulism antitoxin, equine, heptavalent, A through G.

Just a reminder. The product is an equine-based hyperimmune. It's manufactured from equine plasma and contains a mixture of $F(ab')_2$ and Fab antibody fragments that bind to seven serotypes of botulinum neurotoxin. It's important to realize that the mechanism of action is dependent on binding and clearing the toxin from circulation prior to the toxin reaching the nerve endings, because once you have a nerve that has taken up the light chain of the toxin, that nerve is done for for quite a

while.

The indication is for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxins A through G.

Again, we're reviewing this under the Animal Rule because human efficacy studies were not deemed to be feasible or ethical.

Just a reminder. There are several requirements that need to be met in terms of an Animal Rule application.

First of all, there needs to be a reasonably well-understood pathophysiological mechanism. As I've already pointed out. The circulating botulinum neurotoxin acts to block acetylcholine release by cleaving the SNARE proteins and preventing fusion of acetylcholine-containing vesicles at neuromuscular junctions. The sponsor has provided *in vivo* studies that demonstration toxin neutralization of the neurotoxin by the product.

They have demonstrated effectiveness of the product in two animal species. A small animal model, the guinea pig, was used to demonstrate efficacy against all seven serotypes of neurotoxin, whereas the primate was used to confirm the efficacy with a single neurotoxin serotype. I would also point out that the route of administration of the challenge agent was different in these two models. In the guinea pig it was intramuscular injection. In the

rhesus macaque it was an IV infusion of the toxin.

The study endpoints that were used were based on survival at 21 days post-exposure to the toxin.

The PK/PD data that were provided in humans and in the animals will be described in the next presentation by Dr. Staschen.

Just a reminder of what the 2009 guidance suggested as essential data elements in an Animal Rule submission. This includes the characteristics of the chemical, biological, radiological, or nuclear agent. In this case, of course, it’s a biological agent. The toxin is indeed the etiological agent for human botulism. The disease is caused as a result of circulating toxin, so it is really a toxemia.

Host susceptibility: They provided information and demonstrated that guinea pigs and rhesus macaques are susceptible to the neurotoxin -- in the guinea pig, all seven serotypes, in the rhesus macaque, botulinum A. The dose quantities were in the ballpark of what the estimated human lethal might be.

Information was provided on the natural history of disease in these animal models. The guinea pigs and, more so, the rhesus macaques exhibit clinical signs consistent with botulism. Indeed, the clinical signs were used to trigger intervention in their pivotal efficacy

studies.

Characterization of the medical intervention: The product class, as I described, is an $F(ab')_2$/Fab mixture. The mode of action is to neutralize the toxin in circulation.

There are some additional animal efficacy design considerations, which I'll go into in the next slide.

For those that are interested, in the handout there is -- at the bottom of the slide you can see that there's a link to the 2009 Animal Rule guidance.

The design considerations for animal efficacy studies included data elements such as:

• The study endpoint. In the guinea pig and rhesus macaque the endpoint was survival 21 days postexposure to the toxin.

I would also like to point out, as some of the committee has already picked up on, euthanasia was actually used. The animals were not allowed to die on their own. This was due to humane reasons, in consultation with their animal care and use committee. Predefined euthanasia criteria were applied. We have reviewed these and we are satisfied that these were applied evenly across the study. So we are comfortable with the euthanasia criteria s they were applied to the studies.

• The timing of the intervention: In the guinea

pig and rhesus macaque, again, onset of clinical signs. In the guinea pigs the pilot studies initially used the first onset of moderate to severe signs. However, looking at some of the model data, it was decided to push this back to the fourth consecutive observation of a mild or moderate sign of botulism. This was to ensure that the animal was truly symptomatic at time of treatment. In the rhesus macaque, since an intravenous challenge was used, the disease course was much more rapid. The decision there was to treat at the first onset of the clinical signs.

The clinical signs in the rhesus macaques typically involved ptosis, which, you can see, translates pretty well to what can be seen in humans with botulism.

In humans, again, onset of symptoms is when the patients would be treated.

• The route of administration of the product. It’s intravenous in the animal models, as well as in the human.

• In terms of the dose used, a human dose is one vial, regardless of weight, except for pediatric patients and infants. In the animal models they scaled the dose down based on a weight basis. Dr. Staschen will go into that a little bit more in the next presentation.

This slide presents an overview of the studies that were performed to support this biologics license

application. They began with dose-ranging and clinical course studies in the guinea pigs and nonhuman primates, here and here. This coincided with the human PK and safety study, here. These were followed up by PK studies in the guinea pigs and nonhuman primates, here and here. What followed was that these studies allowed the dose of the challenge agent -- in this case, the neurotoxin -- in the guinea pigs they had to do this for all seven serotypes. In the macaque they only had to do it for a single serotype.

But once a challenge was picked based on the treatment window that was available, based on observation of clinical signs in these studies, they moved forward with some pilot studies looking at efficacy in the animal models and concluded with GLP studies, good laboratory practice -- well-controlled, blinded, et cetera, studies -- in both the guinea pig and the nonhuman primate.

There were also some pilot studies performed with the EDB model, as have been described earlier. While the data is supportive, it’s not adequate to demonstrate efficacy. It did provide safety information, however,

Of course, I can’t go on without mentioning the acquisition of the CDC human data under their expanded access program.

As you can see, we have a lot of data from

animal models, as well as some clinical experience in humans, for moving forward.

Initially the goal in the guinea pig model was to establish dose ranging so that a challenge dose could be used for the efficacy studies. A secondary goal was to provide a comparison between the time of onset and intoxication signs and death at the different toxin challenge levels so you can define what your treatment window is going to be. Finally, because the onset of clinical signs is an observational-based endpoint -- your technicians are looking at the animals and it’s up to them to determine whether or not they are sick so that you can initiate treatment -- you can appreciate that there had to be some studies to make sure this could be done in a reproducible way. This was indeed performed in some of these initial studies.

The study I have shown up here on the slide, study 621, was the initial dose-ranging study. You see all seven serotypes plotted here, with survival versus the dose of toxin. Without going into a whole lot of detail, suffice it to say that you can see there is a very steep dose response, such that the LD_{50}, the dose at which 50 percent of the animals die, is not that much different than the dose at which 90 percent of the animals die or the dose at which 99 percent of the animals die. What this means is

that small changes in the dose can have big impacts on these study outcomes. It makes proper use of placebo and control groups critical for these studies.

I would also like to point out that there's a dose dependence in terms of time to onset of clinical signs in the animals. The time to death was also dose-dependent. With higher doses, the animals died more quickly.

Based on these studies, Cangene chose a challenge dose of 1.5x LD_{50} in the guinea pigs and performed some pilot efficacy studies. Study 993 used a 1.5x LD_{50} with serotypes A and E of the toxin. They used a 1x scaled human dose of the product. For this lot, it was 0.16 mL per kg, which was delivered at the first observation of moderate to severe clinical signs. This is going back to what I said earlier. This will change for the pivotal study. An increase in survival was noted in the BAT-treated animals compared to placebo.

They then followed up with another study, 1005, which was performed in the same way, except that the other five serotypes were examined. Again, they saw significant survival in the animals.

These data aren't pivotal, but they are supportive.

The pivotal study: This is the study that we're reviewing and considering as a replacement instead of a

pivotal clinical trial in humans, at least for the guinea pigs. There will be another pivotal study for the nonhuman primates. They are actually testing each individual botulinum neurotoxin serotype individually. You can think of this as seven separate studies performed at different time points. But it’s all under the umbrella of the single study.

A 1.5x IM LD_{50} dose of each toxin was delivered via IM injection into the right hind limb. The studies had two study arms, and study personnel were blinded to what the treatments were. One was an equine-based placebo. The other was BAT, the antitoxin. There were 34 guinea pigs per treatment arm. In this case the treatment trigger was the fourth consecutive observation of moderate to severe signs of botulism in the animals. Again, the thought was t delay the treatment so that we could ensure that the animals were indeed sick. The primary endpoint was survival 21 days post-challenge in the intent-to-treat group.

These are the results. All the challenge animals developed clinical signs consistent with botulism. This is across all seven serotypes. Administration of BAT provided a statistically significant survival benefit against all seven serotypes, even though, as you can see, with serotype G you still had about 50 percent survival in the placebo

group. However, considering you had nearly 100 percent survival in the BAT-treated group, this is still highly statistically significant.

The mean clinical severity scores were lower in the antitoxin treatment arms. This isn't illustrated here. Animals in the BAT treatment arms also had a decreased incidence of severe clinical signs, such as paralysis.

The study has been audited by our biomonitoring review organization and was found to be in compliance. The review personnel have concluded that this study was performed properly, and we're satisfied with the results.

There is additional supportive data that was provided by Cangene for this biologics license application. A treatment study was done at a higher botulinum neurotoxin challenge level, again with all seven serotypes. This is essentially the postexposure model that Chris Sinclair described earlier. In these studies the animals were dosed with a toxin at 4x LD_{50} and then, I believe 12 hours later, were treated with scaled doses, going from a very low dose up to a 1x scaled human dose, of the antitoxin -- excuse me, I'm talking about this study. Sorry, I got my slides mixed up.

This is what I'm talking about now. The postexposure prophylaxis study at 4x IM LD_{50}: The animals were challenged. Twelve hours later, but before they had

symptoms, they were treated with scaled human doses of the antitoxin. What they found was that you achieved greater than 95 percent protection even at one-fifth of the scaled human dose.

Treatment studies were also performed. In this case, the animals were challenged with a 4x LD_{50} botulinum dose, with all seven serotypes again. In this case, at the onset of clinical signs in the animals, treatment was initiated with a 1x scaled BAT dose. However, at this botulinum neurotoxin challenge level, there was no difference in survival observed in the animals between the placebo and BAT groups. There was, however, an increased median time to death in the animals that received the antitoxin.

Sorry for the confusion there.

To summarize the guinea pig data, there was a statistically significant survival advantage with the 1x scaled human BAT dose at a 1.5x IM LD_{50} challenge level for all seven botulinum neurotoxin serotypes in symptomatic guinea pigs. There was no survival advantage, but an increased time to death with a 1x scaled human dose at a 4x LD_{50} challenge level. Postexposure prophylaxis with one-fifth of the human dose was highly effective at preventing death in the animals at a 4x LD_{50} challenge level.

Moving on to the nonhuman primate studies, a

single serotype of toxin is being used as a challenge agent. It's being delivered intravenously. This is actually a fairly rigorous model. The animals get sick quite quickly.

The results from the study returned a result of about 26 mouse IP LD_{50} per kilo as an LD_{50} in the rhesus macaque. This is a little bit lower than some of the published figures, but probably not statistically significant.

The clinical signs observed in the animals, in the rhesus macaques, included ptosis, muscular weakness, respiratory distress, which, you can appreciate, translate quite well into what you might see in a human with botulism. The onset of clinical signs was dose-dependent.

The graphs are simply illustrating the dose response in the rhesus macaque, with dose here versus survival and the time to onset of ptosis, which was usually the first clinical sign observed.

Pilot studies were performed, as were done in the guinea pig. In this case, the pilot efficacy studies used a 1.7 LD_{50} challenge level with BoNT/A. Animals were administered a 1x scaled human dose of BAT or placebo upon the first moderate clinical sign, again which is usually ptosis, weakness, or respiratory distress -- typically ptosis -- a 1x scaled human dose of BAT or equine placebo.

The two studies noted -- in one study they actually saw 100 percent protection in the group that was administered the antitoxin and zero percent survival in the placebo group. In the other study they noted 50 percent survival in the antitoxin group and no survival in the placebo group. Both of these studies were statistically significant, although they did use a small n.

The pivotal rhesus macaque study was designed based on the pilot studies and utilized a 1.7x LD_{50}, again the challenge with BoNT/A delivered by intravenous injection. It was a two-arm study, BAT, or the antitoxin, and placebo. There were 29 nonhuman primates in the antitoxin group and 30 nonhuman primates in the placebo group. Study personnel were blinded to treatment.

Animals were treated at the first moderate clinical sign with a 1x scaled human dose of the antitoxin. Some of you might note that the dose here is slightly different. Different lots of product with slightly different potencies were used between the nonhuman primate and the guinea pig studies.

The animals received nutritional and fluid supportive care. Again, the primary endpoint was survival at 21 days post-challenge in the intent-to-treat group.

All the challenged animals exhibited clinical signs consistent with botulism. The administration of the

antitoxin provided a statistically significant survival benefit compared to placebo. The mean clinical severity scores were lower in the antitoxin treatment arms, and animals in the antitoxin treatment arms also had a decreased incidence of severe clinical signs.

This graph merely illustrates the difference in survival in the intent-to-treat group between placebo and BAT animals. You can see that greater than 40 percent of the animals receiving the antitoxin survived the challenge.

The FDA reviewers looked at this and felt that the study was conducted properly and are satisfied with the results.

An additional piece of data from the study was that the median time to death was increased in the BAT treatment arm. You weren’t able to really do this analysis in the guinea pigs because of the effectiveness of the antitoxin. You couldn’t establish a median time to death in the BAT-treated groups. However, since you had significant numbers of deaths in both treatment arms in this study, you were able to perform that analysis.

So the median time to death was increased in the animals that received the antitoxin, and the mean clinical severity scores were also lower. I think I’ve already said that.

Additional supportive data was provided for the

nonhuman primates, like it was for the guinea pigs. In this case, it was a postexposure prophylaxis model. Animals were challenged and then treated with antitoxin before they became symptomatic. They were challenged with the 4x LD_{50} challenge dose of Bot/A. There were three treatment arms in this study: placebo, one-tenth the scaled human dose, and 1x the scaled human dose. The animals were treated 4 hours after challenge, but before the onset of clinical signs. All animals in the BAT treatment arms survived the study at 14 days post-exposure, even at one-tenth of the scaled human dose.

In summary, what was seen in the nonhuman primates was that a statistically significant increase in survival was observed in the rhesus macaques challenged with 1.7x LD_{50} and administered BAT at onset of clinical signs. There was also 100 percent survival at .1 scaled human dose in a postexposure prophylaxis model using a higher challenge level.

Our conclusions:

• Cangene has adequately addressed the Animal Rule requirements as set forth in the 2009 guidance.

• The reviewers found the design of the animal model studies acceptable and conservative, based on the rapid onset of signs and the narrow treatment window in both animal models. There’s always the challenge of trying

to predict what the human exposure will be in a variety of scenarios. This would include the route of exposure, the serotype, and/or quantity of toxin used in an attack.

• The study outcomes support a conclusion that the animal models are reasonably likely to predict clinical benefit in humans.

That concludes my presentation. Dr. Staschen will now come up and present data on the results of the FDA review of the PK studies and talk about dose modeling.

Agenda Item: Review of Pharmacokinetic Studies

DR. STASCHEN: Good afternoon, ladies and gentlemen. My name is Carl-Michael Staschen. I'm a clinical pharmacology reviewer in the Division of Hematology.

My topic for today is to introduce the review of the pharmacokinetic studies.

This is an outline of my presentation. I will start with an introduction. I will introduce briefly the concept of PK and its established relevance in drug development. Then I'll turn to the pharmacokinetic studies. We have one study in guinea pigs, two in nonhuman primates, one in humans, and then one exposure-response analysis based on modeling and simulation. I will then turn to some comments about the pediatric dosing and will finalize with our conclusions.

Let me please start with the brief introduction: Why do we need pharmacokinetics? First of all, pharmacokinetics provide a mathematical basis to assess the time course of the drug in the body. What do we actually mean by that? There are four distinct phases that we want to understand and interpret: absorption, distribution, metabolism, and excretion. As an example, I have down here a schematic graph with a time on the x-axis, a drug concentration on the y-axis, which depicts a typical single oral dose and a typical concentration/time profile. We do see here in the beginning part, the ascending part, the absorption phase. Then we can say that might be the distribution phase, already then seeing the excretion or elimination phase.

These are not distinct phases, but they blend into each other. It is very important to understand these processes. That is one of the most important things to do in pharmacokinetics.

Again, as already pointed out, a fundamental understanding of these processes is required to design an appropriate drug regimen for patients. Usually it starts very early, in preclinical, then is highlighted in early phases of clinical trial, like Phase I/Phase II. Then it helps to design an optimal and safe dose for Phase III.

One of the paradigms in clinical pharmacology is

that the effectiveness of a dosage regimen is determined by the concentration of the drug. Compared to dose, the drug concentration itself is a much more reliable predictor of the pharmacodynamic biomarkers or, actually, clinical response.

Let’s switch to some relevant basic pharmacokinetic parameters. Why do we need them? You can imagine having a group of data and summarizing these data with a mean. In the same way, we can summarize pharmacokinetic profiles, not with a mean, but with two parameters. These are clearance and volume of distribution. Clearance and volume of distribution and half-life of a drug in blood plasma are primary parameters in clinical pharmacology. We will see later how they relate to these studies.

Derived from these basic parameters are so-called exposure parameters, like AUC, the area under the curve, or C_{max}, the maximal drug concentration, or even C_{min} as the minimum concentration. We’ll see this later in the review.

The PK analysis, in principle, can be done two ways:

• So-called noncompartmental analysis. This is used here in the individual studies.

• So-called compartmental analysis. You need to actually have a little bit more math to it and it’s more

time-consuming.

Those are the ones that you have to use if you model and simulate. And we will see this later, too.

The PK assay that has been used is the mouse neutralization assay. It's an *in vivo* assay. It's the gold standard for botulinum antitoxin and related drugs. Unfortunately, the mouse neutralization assay has a high variability and has a relatively low sensitivity.

Coming back to the overall objective for the submitted PK studies:

• First of all, establish an appropriate exposure metric, like AUC. We want to see that across all studied species and across all seven serotypes tested.

• Use exposure metrics, like AUC, to link the proposed dose to observed clinical-relevant responses. In this case, it's survival and clinical symptoms.

Also the Animal Rule requires some understanding of pharmacokinetics. It says there, in 21 CFR subpart H, the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

Switching now to the pharmacokinetic studies, we'll start with study number 685, the guinea pig study. The objective here was to determine the pharmacokinetics

following IV injections. Study design: As a total, we had 264 animals. They were divided into two groups. One had x1, which means the proposed clinical dose, which is expressed in milliliters per kilogram. The second group had one-fifth of the dose. The collecting time points went out to 12 days post-dose.

As an analysis, the noncompartmental analysis for all seven serotypes has been done. As PK assay, a validated mouse neutralization assay was used.

Here are the results. I only have depicted a couple of them. For the low dose, the serotypes D, E, and F had insufficient data points to make any further conclusions. For serotypes A, B, C, and G, here is the dose. Again, this depicts the clinically proposed dose and this is one-fifth of the dose. Here are the estimated PK parameters. We have clearance over here. We have the AUC and the C_{max}. The color is just to make the reading easier.

All the PK parameters varied based on the antitoxin serotype measured. I'm commenting here only on the one-time dose. The clearance had a range from 2 -- that was the lowest -- serotype D, and serotype E had the highest, nearly 18 milliliter per kilogram per hour. The half-life ranged from about 3 hours to 15 hours, with serotype B. But overall, the results are acceptable and can be used for predicting efficacy in humans.

The next study is FY07, a nonhuman primate study. It was also following single IV administration, serotype A only. Experimental design: We had 12 animals in total, divided into two groups. Here is the scaled human dose in units per kilogram, and x1 stands for the proposed clinical dose. The other group had 5x the proposed clinical dose. Males and females were in equal numbers. The blood collection time points went out to 20 days post-dose.

PK analysis was done again using a noncompartmental analysis for serotype A only, the validated mouse neutralization assay.

Here are the results and the conclusions. Here in this column, we have the botulinum antitoxin dose. Here is 1x the dose, 5x the dose. In this column here are the PK parameters, starting with clearance and volumes, half-life, AUC, and C_{max}. The estimates are reasonable, based on the numbers in parentheses. These are the coefficients of variation, some statistical evaluations. No gender differences were found in the PK. Overall, we have to say that the results are acceptable and can be used for predicting efficacy in humans.

This was another nonhuman primate study, but it was embedded in a PD study that we heard about in the previous report. It was an intervention study, with prevention of mortality, and secondary was to assess the PK

of the botulinum neurotoxin serotype A.

I repeat the design. We had a total of 30 animals, divided into three groups. The dose that was used in unit per kilogram IV was 1x the clinical dose and one-tenth of the clinical dose. The administration was an IV infusion 4 hours post-injection and the evaluation duration was 14 days post-challenge.

The sampling, continuing with the design, was out to 24 hours. As an analysis, a noncompartmental analysis was done, and we had a validated mouse neutralization assay.

We only got submitted the half-life. The half-life for group 1 for the proposed dose was about 5 hours and had a range from 3 to 7 hours. Remarkably, in group 2, having one-tenth of the dose, all PK titers were below the lower limit of quantification, but the pharmacodynamic had 100 percent survival. That would mean that, although unmeasurable PK concentrations, there’s still enough neutralization capacity available to treat the animals.

Our conclusion here is that the mean half-life that’s estimated here is comparable to the 3-hour half-life that was measured without the toxin. Apparently, there is no impact of the botulinum on the half-life of the drug, not the mechanism of action, but actually changing the ADME of BAT. If you look at the molar ratio that we calculated

for BAT and for the toxin, you see that's 10^5 to 10^6. So we have an excess of the drug. We think the toxin here had not an impact on the half-life, on the parameters of the drug.

Overall, the results are acceptable and can be used for predicting efficacy in humans.

Switching to the human PK study, we will hear more on the safety in the next presentation. It was BT-001. The study design was a Phase I, single-center, randomized, double-blind, placebo-controlled study with two parallel arms. The population was 40 healthy volunteers, age 19 to 52, 20 male and 20 female. The primary objective was the assessment of safety. As I said, we will hear more about that in the next presentation. The secondary objective was to assess the PK of all seven botulinum antitoxin serotypes following IV administration.

The route was a single IV infusion over 2 hours, with an incremental increase of the infusion rate. PK sampling was done out to 28 days. PK analysis again was a noncompartmental analysis for all seven serotypes, and the PK assay we used was the validated mouse neutralization assay.

Switching to the results, the pharmacokinetic parameters varied based upon the antitoxin serotype measured. Also here the parameter estimates have

reasonable precision, based on coefficient of variation. Clearance and volume of distribution appear to be similar between both treated groups across all serotypes. That is suggestive of dose linearity of NP-018 over the dose range studied.

The half-life -- and I'm reporting here only the results for one vial, which would be equivalent to 1x the adult dose. The serotype D antitoxin had the shortest mean half-life of about 8 hours, and antitoxin serotype B had the longest mean half-life of about 1.5 days. No gender-related differences have been noticed. Overall, the results are acceptable and can be used for predicting efficacy in humans.

I apologize for the busy slide. I promise I won't read all the numbers out loud to you. But it is an important point that we want to make. This column is the toxin serotype, A through G. I want to point out the different potencies that we have to understand. The nominal potency is the target potency. The potency actual is that that the manufacturer could do. The specification is the minimal potency used, and that's guaranteed by manufacturing.

In the following slides where we use calculations, we are actually referring to the worst-case scenario. We want to pay attention to the specifications,

to the minimal potency possible, to get the worst-case scenario.

That can then be calculated as a dose. Most importantly -- and I have the calculation down here, for people who are interesting -- we can calculate the neutralizing capacity, but based on the minimal potency.

There’s not more that I want to say here.

You’ve seen this slide before, but I want to reiterate the point here -- how the botulinum antitoxin is doing if we compare it to a human dose, not concentration by dose, to a lethal dose. You may be not used to seeing the dose expressed in nanograms. I have some unit comparisons down here. But to make it easier to understand what we actually have measured, we have to rely here and go back to the mouse intraperitoneal LD_{50}. The human dose, as an estimate, is about 40. It’s for serotype A only, where we have that done. The potency, here and the next column, is based on the minimal potency. We can calculate the adult dose, and based on the adult dose, we can calculate the neutralizing capacity and compare that to the human lethal dose, and we see the excess of the drug in the safety factor.

I would like to stay with the neutralizing capacity. In case we suspect or having overt clinical symptoms, we usually have no information about the toxin

exposure. But sometimes we have information about the toxin serum concentration, although that may be later in the course. A better comparison between the toxin serum concentration and the antitoxin neutralizing capacity is done when we compare it to the measured serum concentration, C_{max}, which we'll do in the next slide.

To my best knowledge, based on discussions between Cangene and the US Centers for Disease Control and Prevention, one vial should neutralize a botulinum toxin, serotypes A through G, at achieved serum concentrations between 400 and 20,000 mouse LD_{50} per milliliter. As a comparison, I have listed here some values that are in the literature. This is the botulinum measured in humans. We have the highest ever measured in the United States of 32 LD_{50} per milliliter and the highest worldwide, 160 mouse LD_{50} per milliliter.

So that, compared to 400 to 20,000, seemed to be a reasonable buffer, what to expect.

In the next slide, we actually have calculated the neutralizing capacity of one vial. In the first column, we have the toxin serotypes, A through G. Here are the observed concentrations, mean concentrations, that were evaluated in the PK studies. From these values, we simply calculate the neutralizing capacity. You can see that the minimum here is with E, 940, and the maximum is with

serotype A, about 26,000. The goal is somehow achieved. It is between 400 and 20,000 mouse LD_{50} per milliliter for all serotypes. Even if we would have used minimal potencies here, the neutralizing capacity against the toxin is still between 400 and 20,000 mouse LD_{50} per milliliter for all serotypes.

Turning now to the modeling and simulation, the PK/PD report, the objective is using available preclinical and clinical data, which encompasses guinea pigs, nonhuman primates, and humans, in order to support human dosing regimens of BAT. There are actually two parts to it. The PK part is a compartmental, structural, PK model development, with a special type of analysis here. That is the nonlinear mixed-effects modeling. That is the appropriate analysis to do. The goal was to assess the PK profile for each species and to bring interspecies scaling, and at the same time, simultaneously, use a traditional allometric power model, the same analysis, and scaling compartmental PK parameters between the species.

Once this is done, then the PK/PD part would start with the typical exposure-response model. In this case, just the regression analysis is the appropriate thing to do. It would be to assess the response -- here, survival -- to the toxin in the presence of various exposures -- here, AUC -- of BAT across species. The goal,

again, is to predict the probability of human survival based on the botulinum antitoxin PK.

As a data source, six studies were used, four PK studies, one in guinea pigs, two in nonhuman primates, one in humans, one postexposure prophylaxis PD study in guinea, and one postexposure prophylaxis PD study in nonhuman primates.

Turning to the results right away, for serotype A, a standard 2-compartment model with the structural parameters clearance and volume was estimated. So we had four structural parameters and two allometric parameters in this case. All other six serotypes were analyzed using a standard 3-compartment model, without going into details because of time constraints here. The structural parameters were clearances and volumes. There was an estimation of six structural parameters and two allometric exponents.

The conclusions that we can draw out of that:

• The population predicted parameters are reasonably close to parameters estimated in individual PK studies. That is one of our checks.

• The goodness-of-fit plots, residual analyses, and model validations across all serotypes are acceptable.

Turning now to the exposure-response model, I pointed already out that the logistic regression analysis

is the statistical tool to analyze these data. I have drawn here a simplified graphical representation -- because we have seven serotypes here, seven different results -- just to point out the principle. On the x-axis we have the exposure -- that is, the AUC -- and on the y-axis is the probability of survival.

The animal data -- they have PK data and they have survival data. They are probably here in this area. That's where the regression actually takes place. As a result, you will find a curve being that shape, a sigmoid-shaped curve.

The next thing is, you want to see where the human PK is and the human AUC, the human exposure. It's right up here. Here's the 100 percent survival. It's 0 percent survival. I have plotted it so that we have results of all serotypes, A through G. We have a very high probability of survival based on the logistic regression.

Expressing this in numbers, the predictive probability we have here. In the upper row we have the toxin serotypes, A through G, and we have the probability of survival and percent in the lower row. We can really conclude here that the population PK-based exposure-response analyses predicted high probabilities -- greater than 95 percent -- of human survival across all serotypes based on postexposure prophylactic animal data. Overall,

the results are acceptable.

Turning now to the pediatric dosing, and starting with the infant dose -- infant being less than 1 year -- Cangene has not conducted a pharmacokinetic study or modeling and simulation of BAT in infants. The proposed dose, however, is 10 percent of a adult dose. In order to get a handle on what to expect, we did our own calculation and simply compared neutralizing capacity of one-tenth of an adult dose to an adult human lethal dose, which is the 40 mouse LD_{50} per kilogram. We have this example. In infants, only for serotype A, with 10 percent of an adult dose, the neutralizing capacity is 64,000 mouse LD_{50} per kilogram, based on minimal potency. As you can see, the neutralizing capacity in that dose is several thousand times higher than the actual lethal dose.

The pediatric dose, including ages 1 to 16 -- the sponsor has not conducted a pharmacokinetic study or modeling and simulation of BAT in pediatric patients 1 to 16 years. The proposed pediatric dose is according to the Salisbury rule and is adjusted based on body weight and expressed as percent adult dose. If the body weight is less than 30 kilograms, it is 2x the weight in kilograms, and that expressed in percent of adult dose. If the body weight is between 30 and 70 kilograms, the weight is in kilograms plus 30. That constitutes the percent of the

adult dose. But whatever is higher than 70 is not to exceed one vial per dose, regardless of the body weight.

We also calculated an example and compared it to the estimated human lethal dose of 40 mouse LD_{50} per kilogram. As an example, we took a boy 2 years with an average weight of 30 kilograms, again for serotype A. According to the Salisbury rule, that would bring up a percentage of 26 percent of the adult dose. If we calculate from there the neutralizing capacity, we would come up with a number, 166,000 -- a vast excess of the neutralizing capacity compared to the lethal dose.

Turning now to our comments for pediatric dosing. We have to start out again, that Cangene has not submitted any data to support dosing in pediatric patients. Based on our calculations, it seems that in infants, botulinum antitoxin neutralizing capacity of one-tenth of an adult dose appears to be protective against serotype A. In children, the Salisbury rule for dosing on a body weight basis appears to be protective against serotype A.

We bring in here the post-approval commitment suggestion. Based on lack of data, the agency suggests that Cangene measure BAT concentrations in treated infants and children, and submit the data to the agency in order to evaluate the proposed dose.

Turning now to our conclusions, I would like to

read them out to you:

• Overall, acknowledging the inherent limitations of the PK assay, the design, analyses, and conclusions of pharmacokinetic and pharmacodynamic studies are acceptable.

• Based on the submitted animal and human pharmacokinetic studies and animal efficacy studies, it appears that an adult human dose of an IV infusion of one vial BAT will be efficacious in humans against botulinum toxin.

• The presented data appear to support the proposed adult human dose of one vial of botulinum antitoxin.

• FDA calculations appear to be supportive of the proposed pediatric dosing regimen.

Thank you for your attention.

Agenda Item: Clinical Data in Support of Safety

DR. FEUERSTEIN: Good afternoon. I'm Irwin Feuerstein from the Division of Hematology, Office of Blood Research and Review at CBER.

I will be speaking with you today about the clinical data in support of the safety of heptavalent botulism antitoxin, equine, which hereafter I will be calling BAT.

The FDA analysis of safety was performed using data from the human exposure to BAT submitted in the

original licensing application. This consists of 204 subjects examined under three studies. BT-001 was a pharmacokinetic study with 40 exposures. BT-002, stages A and B, was a pharmacodynamic study, with 16 exposures to BAT in stage B. There was an expanded access treatment program, which was performed in 148 subjects. There was limited pediatric and geriatric exposure, and that occurred only in the expanded access program.

The sources reviewed for the safety data assessment included:

- Study protocols.
- IND safety reports.
- Final individual study reports, including detailed adverse event line listings and clinical case summaries.
- A clinical overview.
- A summary of clinical safety.
- We looked at responses to information requests during the BLA review.

Let’s go through each of the studies one at a time.

BT-001, which hereafter I will call PK, was a pharmacokinetic study. This was a study of PK and safety in 40 normal volunteers at a single center. The subjects were randomized to a one-time intravenous infusion of

either a single or double dose of BAT and followed for 28 days. A single adult dose was one vial of 11.2 mL, and a double adult dose was two vials. There was no placebo control group in this study.

There were an equal number of men and women, with a mean age of 34 years, with an age range of 19 to 52 years.

In the study, routine premedications, such as steroids, antihistamines, antipyretics, were not used. Once subject discontinued therapy because of a moderate allergic reaction, which was characterized by urticaria, pruritis, headache, and fever, during the infusion. Epinephrine, antihistamines, and ibuprofen were administered and the subject recovered.

Adverse event data were collected over 28 days, and during that time subjects were assessed for safety during numerous study visits. Eighteen subjects, total, from both arms reported 53 adverse events. In the single dose arm, nine subjects reported 27 adverse events. In the double dose arm, nine subjects reported 26 adverse events. There were no serious adverse events or deaths reported in the PK study.

Looking at common adverse events in the PK study, we have on the left side the events that occurred in the single-dose arm and on the right side we have the events

that occurred in the double-dose arm. The most common adverse events that occurred were headache, somnolence, urticaria, and down the line.

The most important thing to take away from this slide, comparing left to right, is that there is no dose effect demonstrated on adverse events in the PK trial.

Immunogenicity was defined as equine-specific antibodies against antitoxin that developed by day 28. Fourteen out of the 40 BAT recipients were seropositive at baseline. After treatment, 7 out of 26, or 27 percent, of the remaining baseline seronegative BAT recipients developed antibodies by day 28.

The development of antibodies in some subjects prompted us to look for evidence of serum sickness. Cutaneous findings can be a manifestation of serum sickness, so we looked at the cutaneous adverse events carefully. Urticaria manifested as two episodes in two subjects within 1 hour of the infusion. The first subject presented with urticaria on the left temple and mandible as part of that moderate adverse event that I just described. The second subject developed urticaria on the right forearm, which required no treatment.

Papular rashes manifested also as two episodes in two subjects. The first subject presented with a red bump on his left hand 11 days after BAT, a timing which actually

isn’t bad for serum sickness. But no treatment was required and this just resolved on its own. The second subject presented with a right forearm papule 1 day after BAT. That, too, resolved after just treatment with skin cream.

No other signs and symptoms of serum sickness were reported in these subjects in the PK trial. Because there were no other signs and symptoms, we concluded that these cutaneous events did not represent serum sickness.

Our conclusions for the PK study BT-001 were:

• There was no dose effect observed on the reported adverse events.

• The spectrum of adverse events was consistent with safety reports for other heterologous immunoglobulin products.

Study BT-002, stages A and B, hereafter will be referred to as the pharmacodynamic study, or the PD study. The purpose of these studies was to gather safety data for BAT and to evaluate the effect of prophylactic botulism antitoxin for prevention of paralysis of extensor digitorum brevis foot muscles after direct, intramuscular injection of botulinum toxin. This study was done in two stages sequentially. BT-002 stage A was performed with a previously licensed botulism antitoxin compared with placebo, and BT-002 stage B was performed with Cangene BAT

compared with placebo. The study was done with normal volunteers, with an equal male-to-female ratio. The median age in stage A was 35 years. The median age in stage B was different, 24 years. The age range in stage B was 19 to 49 years.

These studies were two single-center, though different centers, double-blinded, randomized, placebo-controlled preexposure studies. For these, a single vial of a botulism antitoxin or placebo was infused intravenously into the subjects 24 hours before injection of botulism toxin. Stage A was done with a previously licensed BAT product in five subjects versus the placebo, which received five exposures. Stage B was performed with the Cangene BAT in 16 subjects or placebo in 10. Twenty-four hours later, after infusion of the antitoxin, the botulism toxin serotypes A and B were injected IM into the left or the right foot, respectively.

The safety of the Cangene BAT product was assessed in stage B, the PD study, in 26 subjects, 16 of whom received BAT and 10 who received placebo. Again, premedications were not used in this trial. Similar to the PK study, one subject discontinued due to a moderate adverse reaction characterized by urticaria, fever, and chest discomfort during the infusion. The infusion was discontinued. Antihistamines and corticosteroids were

administered, and the subject recovered.

This subject also developed lymphadenopathy at day 10. FDA agreed with the applicant in at least considering this a possible case of mild serum sickness. There were no other signs and symptoms of serum sickness in that patient, but we did count this as a case of serum sickness.

There were no serious adverse events or deaths in the trial with BAT in the PD study.

Adverse event data were collected over 28 days for the study, and subjects were assessed during normal study visits. In the PD study, adverse events were frequent in both arms. In the BAT arm, 14 out of 16, or 88 percent, of the subjects experienced 50 adverse events. This works out to an average of about 3.1 events per subject. In the placebo arm, 10 out of 10, or 100 percent, of the subjects experienced 31 adverse events, which also works out to an average of 3.1 events per subject.

This table displays the most common adverse events in the pharmacodynamic study with BAT. The three events in the orange box -- namely, tonsillar hypertrophy, contusions, and lacerations -- occurred more frequently than placebo, as you can see here. The other events listed below the orange box occurred with approximately equal frequency as the placebo.

Regarding the three highlighted events -- tonsillar hypertrophy, contusions, and lacerations -- our detailed analysis of the temporal relationships and lack of biological plausibility led to the conclusion that these events were most likely not related to the administration of BAT. Because of uncertainties with the causality of some of the adverse events, further safety evaluation in the postmarket setting may be warranted.

Similar to the PK study, immunogenicity in the PD study was defined as the development of equine-specific antibodies against antitoxin by day 28. In stage B, where Cangene BAT was studied, 3 out of 16 subjects in the BAT arm were found to be positive at baseline. After treatment, 4 out of 13, or 31 percent -- which is pretty similar to the 27 percent in the PK study -- of the remaining Cangene BAT recipients who were negative at baseline became positive at day 28.

This is compared with stage A, which studied the previously licensed product. In the threat arm, where all subjects were negative at baseline, 3 out of 5, or 60 percent, of those receiving the previously licensed product developed anti-equine antibodies by day 28. Here too, development of antibodies prompted us to look for other evidence of serum sickness.

There was the one mild case of serum sickness

that we called with the lymphadenopathy at 10 days. That subject did recover without treatment. There was one case of urticaria, which occurred during an acute allergic reaction and responded to treatment. There was also one multifocal rash several weeks after the administration, where the rash occurred after antibiotics were administered for an upper respiratory infection. We didn't consider either of these two latter events to be cases of serum sickness.

So the conclusions for BT-002B:

• First, we considered this a proof-of-concept study. We did not consider this an efficacy study, as the clinical scenario was neither systemic nor symptomatic, but was, rather, localized and prophylactic.

• Looking at the safety aspects of it, most of the adverse events were typical of a heterologous immunoglobulin product. There was the one case of mild serum sickness. There were confounding events seen, including lacerations, contusions, and tonsillar hypertrophy, most of which were plausibly explained by an active study population involved in winter sports and experiencing upper respiratory infections.

The third study we'll look at is an expanded access program. Our numbers will be closer to those of Dr. Babinchak than those of Dr. Rao, because we're looking at

the data as it came in in the original BLA submission.

As of the end of 2011, 148 subjects had been treated under this IND. There were 104 males and 44 females. The study included seven pediatric subjects and 20 geriatric subjects. This was an open-label, uncontrolled study.

The program existed for treatment of subjects symptomatic with a botulism clinical syndrome, with botulism either known or suspected. Ninety-seven out of 148 had a final clinical diagnosis of botulism, and 52 of those 97 clinically diagnosed cases had a laboratory diagnosis with serotype documented. The premedication status in these subjects was unknown.

Safety data was available from 146 out of 148 subjects. Treatment-related adverse events were reported in 18, or 12 percent, of the subjects. The most common adverse events were fever in 6 percent, rash in 2 percent, nausea and edema in 1 percent, and less than 1 percent each of some more significant adverse events, including bronchospasm, bradycardia/asystole, and serum sickness. There were other adverse events that didn’t make the chart.

Infusion was discontinued in one subject due to a serious adverse event, which you have seen already and I will talk about. There was one case of mild serum sickness, who later died from unknown causes. Six out of

148 subjects ultimately died, which works out to about 4 percent. Four out of the six deaths were diagnosed with botulism. Five out of the six deaths were at least 64 years old.

Information on the individual subjects was limited. However, no causal relationship was established between the deaths and the administration of BAT.

This is a busy slide about the six deaths reported. In most of the cases, the cause of death was not related to BAT. In the first case with mild serum sickness, the exact cause of death is unknown, but after review was considered unlikely to be directly related to BAT or to the serum sickness. In the fourth case, that subject died 7 days after BAT with Guillain-Barre syndrome, but the exact cause of death in that person is unknown.

In the pediatric subjects, there were seven, aged 10 days to 15 years. Median age was 5 years. Two out of the seven, or 29 percent, had adverse events. There is the one serious adverse event, which I'll detail on the next slide. There was one case of a child with preexisting fever which worsened around the drug infusion, up to a maximum of 101.8 degrees, and recovered. There was one infant who did receive the product who had no adverse reactions. No deaths were seen in the pediatric population.

The serious adverse event was a 10-year-old male, who was already intubated from respiratory paralysis secondary to his botulism. He had no history of prior cardiovascular disease or arrhythmia. During the infusion, bradycardia developed, which led to asystole, which necessitated cardiopulmonary resuscitation and intravenous epinephrine. Once the child was resuscitated, the infusion was restarted. Bradycardia again ensued, which was again treated with intravenous epinephrine. At that point the infusion was terminated, the child having received 70 percent of the intended pediatric dose.

This was considered serious, unexpected, and probably related because of the positive rechallenge.

Because the safety data are limited, it is likely that some common adverse events may have not been detected in the three clinical studies assessed for safety. Therefore, collection of additional postmarketing safety data is warranted.

In the sporadic cases, what we're asking for is enhanced active surveillance in the form of 15-day reports. These will be submitted for all serious events and for any non-serious events related to bradycardia, allergic reaction, serum sickness, febrile reactions, or tonsillar hypertrophy.

We are also looking at a registry as a required

postmarketing safety study under Section 901 FDAAA 2007 Title IX. This can be modeled after the existing expanded access program and run for a minimum of three years.

In the event of a mass exposure, the Animal Rule requires postmarketing studies to monitor safety and efficacy of the products approved under the rule, when such studies become ethical and feasible.

To address this requirement, the agency proposes that Cangene reactivate the previously established registry and expand data collection to all confirmed and suspected botulism patients, to capture safety and efficacy data in any mass exposure scenario. This would include analysis of botulism patients treated and not treated with BAT, efficacy endpoints, including death and length of care, and safety endpoints, including adverse events occurring within 30 days of the last infusion.

Our safety conclusions are that the safety profile for BAT appears acceptable relative to the expected benefit. There were two cases of serum sickness. There were two moderate allergic reactions and one serious hemodynamic reaction. There were no thromboses, anaphylaxis, or hemolysis. Deaths could not be attributed to the BAT.

Serum sickness, allergic reactions, and bradycardia can be addressed in the Warnings and

Precautions sections of the label.

Finally, safety should be further evaluated in the postmarket setting.

Thanks.

DR. JACKSON: Thank you very much, Dr. Feuerstein.

We have a few minutes now for specific questions for the presenters. Then we'll have an open public hearing for comments, take a short break, and then we'll do the committee discussion.

Do committee members have specific questions?

DR. SIMON: I just have a concern for the practicality of doing a registry in the midst of a mass casualty situation. I did see that the rule actually says "when ethical and feasible." Is that what FDA is looking at, that it would be required, but with the understanding that it would be ethical and feasible?

DR. STASCHEN: Are we with the questions now? What about the summary?

DR. JACKSON: Oh, I'm sorry. You had a summary. I'm sorry. Go ahead.

Agenda Item: Review Summary

DR. FISHER: That's quite all right.

I'll be very brief. What I'd like to do is just summarize the FDA review findings.

One thing I want you to consider is the criteria under which we're reviewing these studies:

• The animal studies must be adequate and well controlled.

• The mechanism of injury should be reasonably well understood.

• More than one species should be used to demonstrate the desired effect, which should be the prevention of major morbidity or survival.

• Finally, there should be pharmacokinetic and pharmacodynamic data sufficient to allow selection of an effective dose in humans.

The animal efficacy studies that were performed in two species were blinded, placebo-controlled, adequately powered, and were performed under good laboratory practices, which includes the use of predefined euthanasia criteria.

The studies were performed with intravenous or intramuscular injection of the challenge agent, botulinum neurotoxin. The animals that were challenged demonstrated clinical signs consistent with botulism. Treatment with the antitoxin was initiated based on observation of clinical signs in the animals prior to treatment. The study outcomes, based on our estimate, support a conclusion of efficacy.

In terms of pharmacokinetics, studies were performed in humans, guinea pigs, and the rhesus macaques. Modeling and simulation suggests that the proposed human dose offers an adequate potency buffer, based upon estimated human lethal doses of the toxin.

The human safety conclusions, based on three clinical trials and one expanded access protocol:

• Immunogenicity was observed, but not unexpected.

• We are requesting additional safety studies as postmarketing requirements.

• The available safety profile for the antitoxin is acceptable relative to the expected benefit.

Which I'll describe here. Botulism is a life-threatening condition. Data from well-controlled animal studies, which were outlined here, demonstrate that the antitoxin substantially improves survival. It is anticipated that treatment in symptomatic humans should reduce the need for or duration of hospitalization and mechanical ventilation.

The risk of severe allergic reactions and serum sickness is relatively low and can be mitigated with premedication. In any case, these conditions are responsive to treatment if they do occur. Finally, overall, based upon its assessment, the agency considers

that the benefits exceed the risks associated with use of the antitoxin to treat symptomatic botulism.

I would also like to point out that there is an unmet medical need. There is no vaccine available for preexposure prophylaxis of botulism. There is no licensed therapeutic for adult botulism. Again, I'll reiterate that botulism is a serious and life-threatening condition.

Should I do the questions?

DR. JACKSON: Why don't we do that when we get to the committee discussion? We'll take some questions now for the speakers.

Toby asked one question. Maybe we could start with that one.

Agenda Item: Questions for Speakers

DR. JACKSON: The question, I believe, was, in terms of the postmarketing studies, the studies were to be performed if they were feasible and ethical. Correct?

DR. SIMON: Related to the mass casualty situation. The others are fine. But I'm assuming in a mass casualty, it's going to be very difficult to do a registry. I notice that the Animal Rule states "when ethical and feasible," which gives me some reassurance, if that's the FDA's interpretation.

DR. JACKSON: It's our intent to attempt to collect this data. That's the purpose of the registry.

DR. GOLDING: Basil Golding.

In the CFR, which I'm holding in my hand here, it states that the FDA also retains the discretion to remove specific post-approval requirements upon review of a petition submitted by the sponsor in accordance -- and I won't go on and on. Essentially there is a kick-out clause. The way I read that is, if in a mass exposure it's not feasible to collect the data, then the company needs to make that petition to the FDA to waive that requirement. But our expectation is that a good-faith effort will be made to collect the data, for obvious reasons.

DR. JACKSON: I have a question for Dr. Staschen. On your slide 25, on the modeling, you showed the predicted probabilities of human survival based on, quote, "postexposure prophylactic animal studies." Is that giving BAT 4 hours post-challenge or is that giving BAT at the first symptoms?

DR. STASCHEN: It's not the treatment. It's not the symptoms. It's given 4 hours after the toxin.

DR. JACKSON: Okay.

DR. DEMETRIADES: The efficacy in the animal studies is really very impressive. But I'm still concerned, because the antitoxin was given at the moment they saw the onset of clinical signs. In the clinical scenario, we'll be lucky if we administer the medication 8

to 12 hours later. Why do I say this? In critical care, we know from a lot of experience that certain medications, if given very quickly -- within the first 1 or 2 hours -- they are good and they save lives. If given later on, they have a negative effect -- just to give you an example, tranexamic acid, which is an antifibrinolytic agent. If given within 3 hours of the onset of bleeding, it improves survival. If given after 3 hours, it makes survival significantly lower.

So I would suggest that at some stage the company might want to look into that and give the antitoxin 8 hours, 12 hours after exposure. I'm not saying to hold the approval, but I think it's ideal to optimize outcomes by defining the ideal time of administration.

Thank you.

DR. JACKSON: Along those same lines, the data Dr. Staschen showed on probability of survival, et cetera -- it looks really good if it's given prophylactically before the challenge or shortly thereafter, but waiting until there are symptoms, clearly the efficacy could be quite variable. What was used here -- just like in vaccine efficacy studies, it depends on the challenge dose. In the guinea pig data you showed where you gave four times the lethal dose and you waited to treat at symptoms, they all died, whether they got BAT or

didn’t get BAT.

If we’re all exposed to some mass bioterrorist attack where we get ten times the lethal dose, it may not work whatsoever, because enough molecules are bound to these nerve endings that at that point it won’t be effective.

So the data that’s being presented, in some way -- I don't want to say it’s a best-case scenario, but it’s a limited scenario. As you were saying, you’re giving it at the first symptoms, and, of course, in reality, it’s going to be later. You do have the expanded access program that CDC presented. That’s reassuring. But I don't get the impression that -- if you get a high enough dose, I’m not sure this would be effective at all.

DR. FISHER: That is a potential risk --

DR. JACKSON: If you wait until symptoms.

DR. FISHER: That is a potential risk. However, the fact that you observed greater than 40 percent survival in the nonhuman primate model, which had a very short difference in time between time of onset of symptoms versus time to death, I think helps to go to that. Remember, these animals didn’t receive much in the way of supportive care. The nonhuman primates did receive nutritional support and fluid support. The guinea pigs, not so much.

You can imagine that there will likely be a

spectrum of outcomes and it will probably be depending on time of treatment and the amount of toxin received.

DR. STASCHEN: I would like to comment briefly on the modeling and simulation. I see that's getting a lot of attention here.

Cangene pointed out -- and we agreed to that -- that it is supportive, supportive only. It's not hard evidence. We look at it as supportive only -- very supportive, but nothing more.

What we like to establish is the neutralizing capacity based on the C_{max} values, and then how that looks and relates to the observed toxin concentrations in humans. That is the more serious approach that we took.

Again, we know it is post-prophylactic, and the data may have changed a little bit -- not much, I assume, if there would be have been the treatment studies included. But it is supportive evidence only.

DR. BONILLA: Immunogenicity of the product is expected to some extent, but in the data that you showed, somewhere between 30 and 40 percent of people were, quote/unquote, seropositive in the assay even prior to receiving the drugs. It seems that that assay perhaps is not very well suited to actually tell you the true rate of seroconversion.

DR. FEUERSTEIN: It didn't predict adverse

events.

DR. RHEE: I think the specific questions that are posed to this advisory committee are fairly clear, and answered in many degrees. One of the parts that I don't think has been emphasized is that it seems to really reduce morbidity, time on a ventilator -- shortened that in humans. I think everybody is fairly convinced of that. We don't know if it saves lives per se because of critical care and ventilator use. I know that I certainly would want this drug if I got botulism and it meant that I was going to be saved a couple of weeks on a ventilator, sure.

I guess the real issue is, from the animal studies, it shows that it’s fairly safe and we don't have crazy reactions to this stuff. But from the CDC data and clinical use, if I’m not mistaken, it killed one kid. We were able to get him back. But it seems like that drug was specifically responsible for, for whatever reason, killing that 10-year-old kid and then bringing him back.

I guess one out of 143 events -- that is the one thing that’s playing in my mind. All the other events seem to be fairly similar and don't really alarm me as to the minor adverse events, serum sickness and so on like that. That’s something I would probably be willing to take as a consequence. But how often are we going to get this infusion and then bradycardia and going into asystole, I

guess I the main question.

DR. FEUERSTEIN: Thanks for the comment. We're looking at that carefully in the postmarket proposals. We want to be on top of that.

DR. SOBEL: Echoing Dr. Rhee's comment, FDA is recommending three-year postmarketing follow-up. The incidence, if you will, or the proportion of pediatric cases with complications, by virtue of this one case of a severe reaction in a child, is much higher. If I recall the number of children that are actually receiving this medication, it's on the order of about three children per year.

So I think you would want to accumulate a large number of pediatric cases to really get comfortable with the safety of this medication. To me, that would argue more than three years, which would be on the order of another 15 children. I think one would want to go far out and accumulate a large number of pediatric cases to feel comfortable -- if not statistically persuaded, at least impressionistically persuaded that it is safe enough to treat children.

DR. FISHER: I think the actual details of what the registry is going to be are still in negotiations. One of the things could be to consider a certain minimum number of pediatric cases or a three-year period, something along

those lines. That certainly can be taken into consideration.

DR. RHEE: In regard to the question about putting the burden of the registry on the drug company, I think it's fine -- I mean, the drug is still going to be administered through CDC and you’re going to have to call them. They are the ones that are going to have to release the drug. Then the actual follow-up of exact registry details is going to be put on the company. I think three years is a good place to start, rather than saying, let’s calculate out five, ten, 15 years. Three years is a good place to start, because I’m sure that after three years, you’ll look at the data and say, we need more, we need less, this is adequate, or in this population of people we don't have enough, we would like to do more, and so on. So I think the three-year time period is probably a good place to start.

DR. GOLDING: This is under negotiation. We are also working with our Office of Biostatistics and Epidemiology, and with Cangene. We’ll take a lot of these comments to heart.

But I think it’s very reasonable to suggest that we have a minimum number of pediatric patients and also that after the three years, we reassess the situation and decide to what extent it's needed to carry on with the

registry.

But I would also like to point out that Dr. Rao from the CDC made it very clear that without the FDA's requirement, the CDC would carry on beyond the three years to collect data on these patients.

Am I correct, Dr. Rao? For every patient that's given the product, you have contact with the physician and you follow up to find out if there are adverse events. We should have a minimum number of requirements for the registry, but we will have follow-up after the registry ends, in any case.

DR. RAO: We do follow up as far as finding out what's going on with the public health investigation. But as far as adverse events go, we had funding during the time that H-BAT was being released to have someone dedicated to actively following up and making sure we were getting all that paperwork back. But we won't have that funding, and so we won't have complete data. It will be just like pre-H-BAT.

DR. JACKSON: All right. I've got to make a comment about the open public hearing. Then we'll take a short break and then we'll come back and go through the questions.

DR. FISHER: In fact, it's up to you. If you would like to read them, that's perfectly okay.

DR. JACKSON: That’s fine. I can do that. Just have them up on the slide so we can do that.

Agenda Item: Open Public Hearing

DR. JACKSON: So if I may read this open public hearing announcement for particular matters involving specific parties.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual’s presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor’s payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of a financial relationships at the beginning of your statement, it will not preclude you from speaking.

Do we have anyone from the public who wishes to make a statement or presentation?

LCDR EMERY: We have no one that has requested time to make an open public hearing statement, but we have the time available if there is anyone in the audience who would like to make a presentation.

(No response)

DR. JACKSON: Okay. Then let's take a short ten-minute break. We'll be able to leave, potentially, early this meeting. We'll start at a little after 3:00.

(Brief recess)

Agenda Item: Open Committee Discussion

DR. JACKSON: The first question: Do the results from the efficacy studies of botulism antitoxin heptavalent, A, B, C, D, E, F, G, equine, in guinea pigs and nonhuman primates provide sufficient evidence that the product is reasonably likely to provide clinical benefit for the treatment of humans with symptomatic botulism?

So we're talking specifically about once you have symptoms. Would someone like to voice an opinion on this, to start with? Yes, Toby.

DR. SIMON: I'll go ahead. I think we've been presented with sufficient evidence and support by the FDA. So I would think it's a pretty clear yes on number 1.

DR. DEMETRIADES: It states there "reasonably

likely to provide clinical benefit." I think it's a very appropriate statement, and I would support it.

DR. JACKSON: I think the data showing whether it's length of stay or on a ventilator in the human studies were very supportive of this. Obviously, as you pointed out before, the clinical benefit may be very dependent on the dose, amount of toxin received, and the timing of the administration, once symptomatic. But it would seem that there would be at least some proportion that would likely benefit from administration of this product clinically.

DR. DEMETRIADES: Mr. Chairman, is it possible to state this concern about the timing, dosing, and make a recommendation for another experimental animal study?

DR. JACKSON: I'm not sure, exactly, of the rules here. But I think, as a recommendation, if we want to add something to suggest how it might be more efficacious or effective, we can probably do that. If you want to say that -- and in terms of the earlier it can be given, whether it's easier access to the product or recommending that somehow we're able to make a diagnosis faster -- all of those things would clearly enhance the efficacy, it sounds like, of this product.

DR. KUEHNERT: I just want to point out that this specific question -- is it reasonably likely to provide clinical benefit in humans? -- given the clinical scenario,

which we can’t control much of, I think there’s evidence that this helps clinically. But specifically answering this question itself, the problem is that in the animals they looked at survival and didn’t really look morbidity or the length of paralysis. Since it seems like we do reasonably well with survival in humans without it anyway -- it’s just that they have to be on a ventilator for a longer period of time. They didn’t really look at the main issue, because it’s really hard to provide survival difference in humans because there are not many deaths from this anyway. The clinical efficacy is really the length of paralysis. It didn’t specifically address that.

It’s just a comment.

DR. STEVENS: I just want to bring it back in terms of the Animal Rule efficacy criteria. As both Cangene and FDA went through pretty thoroughly in terms of what efficacy is -- stating that these animals were done under well-controlled trials, the mechanism of injury is reasonably well understood, and going through each of those -- I thought that was well presented. It’s not all times that you get this to follow all of these in terms of presenting data for each. They have a history with this product.

DR. JACKSON: Other comments?

(No response)

So I think the answer to the first question is yes.

DR. GOLDING: We need to have a vote on this, please.

DR. JACKSON: Oh, I'm sorry.

All in favor of this recommendation that it will likely provide clinical benefit for the treatment of humans with symptomatic botulism -- I guess you vote yes, abstain, or no.

(The vote was taken.)

LCDR EMERY: The committee has voted a majority as yes. Let me read the names so it is lodged in the record.

Dr. Jackson, yes.

Mr. Corey Dubin, yes.

Dr. Sobel, yes.

Dr. Adler, yes.

Dr. Bonilla, yes.

Dr. Schexneider, yes.

Dr. Rhee, yes.

Dr. Stowell, yes.

Dr. Maguire, yes.

Dr. Kuehnert, yes.

Dr. Demetriades, yes.

Dr. Durkalski, yes.

Dr. Gilcher, yes.

Dr. Kuzma, yes.

DR. JACKSON: All right, question number 2: Do the results from safety studies in healthy human volunteers, efficacy studies in animal models, and clinical data from CDC's use of BAT under IND expanded access protocol support an acceptable risk-to-benefit profile for use of BAT?

Comments on this one?

We did see a number of adverse reactions. They tended to be mild. In the two groups, they were equal in each group, although they were, like, 88 percent in each group. In the other -- I think it was the -- it was 12.3 percent we saw in the -- I can't remember if that was the BAT-2 study or the expanded access program. But they were, in any case, relatively mild and could be managed. There was the one child, though, that had a real concern. FDA has said that they would take this into account in terms of the labeling of the product so that clinicians would be aware of that and monitor for that purpose.

Otherwise, it looks very similar to other types of reactions seen with immune globulin products overall.

PARTICIPANT: I would just like to state for the record that a case of asystole in one of seven children

receiving this medication is of grave concern. I personally feel that the risk-to-benefit ratio justifies the licensing of this product for children, but I think that there is a requirement that thorough evaluation into the future, post-licensing, continue, especially for children.

DR. KUZMA: I'm still concerned about children and the risk-benefit ratio for children. I'm not sure what to make of it, especially given that there's a product out there that seems to be okay for children that could be ramped up, perhaps.

PARTICIPANT: I want to respond specifically to the issue about the other product, being BabyBIG. Dr. Arnon, of course, is the undisputed authority on BabyBIG. But the amount of antitoxin available in BabyBIG is two orders of magnitude below that of this proposed product. We have very few, but nevertheless very telling cases, published cases, of children, especially infants, who were misdiagnosed with infant botulism and were subsequently shown to have foodborne botulism. There's a paper by Armada et al., from 2004, 2005, which is the classic. It shows basically that treating an infant with foodborne botulism, with a massive dose of toxin type A, with BabyBIG, under the assumption that the child had infant botulism, produced no clinical response, whereas treatment

subsequently with what was then the available equine antitoxin at a much higher dose did produce a result.

So, really, I don't think that BabyBIG can be considered a substitute in non-infant botulism syndromes.

DR. KUZMA: What about the older product, the BAT ABE one? I know it’s no longer in production, but --

DR. FISHER: It’s no longer available, period.

DR. KUZMA: And it couldn’t be made re-available?

DR. FISHER: The manufacturer does not manufacture that product any longer.

I would like to clear up perhaps a misconception about BabyBIG. It’s licensed for use in infant botulism for infants under 1 year of age. In addition, the potency is considerably less. I believe it’s on the order of -- I can’t do the math in my head. Dr. Arnon, thank you.

DR. ARNON: It’s two orders of magnitude below that of this product under discussion.

DR. FISHER: Exactly.

DR. KUZMA: What’s the safety of the older product on children? I would like to just know. We used it for, what, ten years? What’s the safety of BAT-ABE on children, and why didn’t we reproduce that instead of producing something new?

That’s my question. If anybody can answer that, that would be great.

DR. KELLEY: The old product was produced by a manufacturer who no longer even has the facilities to make the product.

Cynthia Kelley, FDA.

DR. KUZMA: But we know how to make it. I was a biochemist, so -- you know how to make it. It has been published in the literature. Somebody knows how to make it.

DR. KELLEY: But we don't make it. The manufacturer made the business decision not to make it anymore many years ago.

DR. KUZMA: Okay, but the government is funding the making of this. My question is, why can’t resources be put into making an older product that was safe, if it was safe? I’m not sure if it was or not. That’s why I’d like to see data.

PARTICIPANT: The Cangene product is made from horses. The old product was made from horses. They immunized the horses with the toxoid and then the toxin when the horse is protected. So the actual manufacturing process is, to some extent, similar. But it’s another manufacturer, and each manufacturer has its own way of doing things.

But the basic principle of the manufacture -- horses are immunized, the plasma is taken from the horses,

the plasma is pooled, and the plasma then goes into a manufacturing facility. The critical steps of manufacture are the pepsin digestion and looking at the potency. All of those steps are very similar to what was done before.

We can't resurrect a manufacturing site that decides that it's no longer manufacturing. We can try and replicate it, and to the extent possible, with oversight of the manufacturing by Cangene, we have worked with them to try and produce a product that is, as far as we can tell, well characterized and the best they can do under the circumstances.

DR. JACKSON: What about safety data in pediatrics with the old product that she asked about? Do you know offhand or no?

DR. EPSTEIN: Before we try to answer that, let me just add a few more comments. The requirement for manufacture of a product for the National Stockpile was that it should have specificities for neurotoxins A through G. The prior product did not. It was A, B, and, to some extent, under IND, E. So it wouldn't meet the current requirement. There's a distinct advantage in having a more polyvalent, especially heptavalent, product.

So that's one point.

The second point is that this product actually has a better purity profile. The previous product was

intended to be a F(ab)2 product, but, in fact, had a significant, I would say, contamination with full-length immune globulin, which implied prima facie that it was likely more immunogenic, more likely to produce serum sickness.

There are heterologous amino acid sequences in the constant regions of the Fab portion, so it’s not surprising that humans develop antibodies even to the Fab and F(ab)2. But it would be that much worse with the Fc portion, which is essentially gone in the current product.

So I think those two points need to be kept in mind, the fact that we want a heptavalent product in the stockpile -- the old product -- there’s no point in making it, because it’s not going to meet the current requirement for a counterterrorism product.

As far as the safety profile in pediatric use, I just want to emphasize one thing, which is that, as has been said, BabyBIG is really not suitable generally for pediatric use because it doesn’t have sufficient potency and volumes. Dr. Arnon rose to the mike to explain that point, and if you would like to hear the detail, we can bring him back.

DR. KUZMA: No. I understand that.

DR. EPSTEIN: Okay. So then can we comment on the safety profile in pediatric use? Can CDC comment?

DR. KUZMA: If the old product had the same safety issues, then it’s the best we can do, right?

DR. SOBEL: I don't recall the specific data for pediatric patients and for complications from treatment with the old AB or ABE formulations that were in use for about 20 years. But I do not recall that the profile was any different for children than it was for adults.

DR. KUZMA: Thank you.

DR. JACKSON: Many adverse events, especially with IV route of administration, are related to the rate of infusion, whether it’s a drug or a product. I didn’t hear any data presented about that here. Was it consistently done in the children? I don't know, CDC, whether you know what you recommend, how it is given, like in the access program, like in those pediatric cases? Do you know that they all were administered at the same infusion rates and that sort of thing? Should it potentially be a slower infusion rate for children?

DR. RAO: It actually is infused at a slower rate for pediatric patients. I can’t speak to -- I know that there was a two-dosing regimen earlier on with the first two cases. That has changed since then. Currently the protocol is for it to be a slower infusion rate, for those patients to be given various antihistamines, things like that, before the administration of antitoxin to minimize

the chance of adverse events.

DR. JACKSON: It’s just something that might be worth looking at. Reactions are often related to infusion rates, no doubt about it.

DR. SOBEL: One other final observation in this respect. The old products, AB, ABE, until approximately 1990, they were given in doses of, first, four vials and then, subsequently, two vials. So we’re talking about doses that were two to four times the dose that was used in the past ten years or so. In terms of actual protein content, that is, I believe, substantially higher than that of this H-BAT product. The safety profile was not substantially different in children that it was in adults during the periods in which those old products were administered in different doses.

DR. JACKSON: Other comments?

(No response)

From the couple comments we have heard so far, a number have thought that this would support this as an acceptable risk-to-benefit profile for use of BAT, but clearly with children, there is the major concern that there be longer or better follow-up in these children. That would be the main recommendation, it sounds like, as part of this.

Any other comments? Are we ready to vote, then?

Okay, let’s see if we can do this.

(The vote was taken.)

I guess we do have the option to ask industry if they want to make any comment before you see the vote. Any comment on the comments that were just made on this issue about safety in children or infusion rates or anything?

DR. FISHER: I think we had a good discussion, and I think the company is aware of it. I think there were some unusual things with the 10-year-old child, but obviously the careful watching into the future makes sense. I do believe that the acceptable, considering the benefit, has been well demonstrated.

LCDR EMERY: The voting is unanimous as yes. I will read the names.

Dr. Brooks [Jackson], yes.

Mr. Corey Dubin, yes.

Dr. Sobel, yes.

Dr. Adler, yes.

Dr. Bonilla, yes.

Dr. Schexneider, yes.

Dr. Rhee, yes.

Dr. Stowell, yes.

Dr. Maguire, yes.

Dr. Kuehnert, yes.

Dr. Demetriades, yes.

Dr. Durkalski, yes.

Dr. Gilcher, yes.

Dr. Kuzma, yes.

There are no abstentions and no noes.

DR. JACKSON: Thank you, Bryan.

The next question, number 3: Do the animal studies and simulation modeling adequately support the proposed dosing in humans (a) for adults, (b) for children?

We have very little data here.

DR. STEVENS: I can speak to the modeling aspect. In terms of adults, there was consistency observed, supporting the proposed dosing in adults. It was consistent and data was submitted.

For children, there is no data. It would be speculation.

DR. JACKSON: Dr. Staschen did present some extrapolation, I think, in terms of whether it was on the body weight, the Salisbury criteria versus strictly body weight, kilogram.

DR. STEVENS: I am not as familiar with the Salisbury. I did ask another one of the members if they were. We had not heard of this type of dosing for pediatric. The underlying basis for that calculation, I understand, is on body weight, but, really, this stays within the systemic circulation. So I don't know if that

translation is adequate to extrapolate, in terms of just a strict extrapolation.

DR. SOBEL: For many decades, body weight or surface area types of schemes have been used for pediatrics. They have been best-guess, from the practicing clinical consultant’s perspective. It is not difficult to imagine a scenario where a child could ingest a massive dose of botulinum toxin from a contaminated food. Public health investigators on a regular basis identify foods and outbreaks that have very high toxin levels. It’s that same dose of toxin in a child as it is in an adult.

One could speculate this way and that, but I think the data is sparse and, while I favor moving ahead with licensure, I think that it has to require very intensive monitoring of children and very intensive monitoring of the effectiveness of this proposed dosing regimen. We just don't know, and the data needs to be systematically collected prospectively to determine if it really meets the needs.

DR. EPSTEIN: Just two comments. There will be a later question about FDA’s suggestion to the company that blood levels be obtained in the instance of pediatric dosing in order to confirm the extrapolation based on the modeling. That’s one point.

The other point is, of course, everyone realizes

there is uncertainty about what the exposure dose could be in a given outbreak. It may be unprecedented, of course, in a mass event. But the general concept is that if the patient continue to progress with development of symptoms, then you give another dose. So on the one hand, there’s uncertainty about, perhaps, adequacy of dose based on extrapolations, but on the other hand, if we think that it neutralizes toxin, doctors can give more. And that’s exactly what they do in practice.

DR. JACKSON: I don't know if Dr. Staschen is still here. The way that I looked at it, I thought that on a kilogram basis, it’s a little higher amount per kilogram for the children than in the adult -- not a lot higher, but it is slightly higher.

DR. STASCHEN: Yes. We just compared the dose on a dose basis and the neutralizing capacity, and set this in reference to the estimated human lethal dose. There was more than 1,000-fold excess of the botulinum antitoxin.

DR. JACKSON: Data on whether the half-life might be different in a child than in an adult, of the toxin?

DR. STASCHEN: It may be, but without any data, we can’t really tell.

DR. JACKSON: Any other comments. Dr. Kuzma.

DR. KUZMA: I was just going to ask, are we going to vote on these separately, a and b?

DR. JACKSON: I think we should. Is that okay?

Any other comments?

(No response)

Okay, let's vote on the first one for adults, about whether the animal studies and simulation modeling adequately support the proposed dosing in humans, for adults.

(The vote was taken.)

LCDR EMERY: The committee has voted. It's unanimous at 14 yes, zero abstentions, and zero noes. I will, for the record, call out the names.

Dr. Jackson, yes.

Mr. Corey Dubin, yes.

Dr. Sobel, yes.

Dr. Adler, yes.

Dr. Bonilla, yes.

Dr. Schexneider, yes.

Dr. Rhee, yes.

Dr. Stowell, yes.

Dr. Maguire, yes.

Dr. Kuehnert, yes.

Dr. Demetriades, yes.

Dr. Durkalski, yes.

Dr. Gilcher, yes.

Dr. Kuzma, yes.

DR. JACKSON: Before we vote on the second question, maybe I could ask Dr. Epstein, if we were to say no, but this were approved, clinicians could still use this, potentially, as an off-label indication? If people think that there’s really not data to support it one way or the other, but obviously there could be potential benefit, what would be the implications for the CDC, who would be actively distributing this product or not?

DR. EPSTEIN: I’ll let Dr. Rao speak to this, but I think that the formal legal framework would be that we would probably want it still under IND for the pediatric use. Of course, it’s legal for licensed products to be used off-label. That’s at medical discretion. But given that it would have to be released by the CDC and that, generally, the public health agencies don't promote off-label use, it gets a little bit tricky. More likely than not, we would talk about keeping the pediatric use under IND. But we have to cross that bridge.

DR. RAO: I was going to say the same thing. To keep it under IND would be the way to release it. We get a lot of resistance from pediatricians even right now because it’s under IND and it’s not a licensed product. People are always nervous about accepting it. Sometimes when we release the antitoxin, they won’t even administer it to the patient. They’ll do all these other things and buy time

while they are deciding whether or not to even give an initial dose.

DR. JACKSON: But if it were kept under IND, they would still go to the CDC for that program, and so they would still potentially have access to it, and you would use the proposed dosing here, but it would be under IND.

DR. RAO: That’s right.

DR. SOBEL: Before we go in that direction, I think we should deal with the practicality issues. I think we have done the best -- the company and the agency and so forth -- with the data that are available. The likelihood that in any period of IND we would get better I think is small, and as we have just heard, it becomes a deterrent to its use in some patients in the minds of some physicians, and we may have deaths or bad impacts on health care, on the care of these children, because of it.

So I would speak to a yes vote, given the limitations that are inherent in trying to get this information in children.

DR. JACKSON: But my understanding is, even for adults, it would still have to be at the CDC.

DR. SOBEL: The CDC is the access point, but they would be dealing with a licensed product rather than a product under IND --

DR. JACKSON: I understand, but --

DR. SOBEL: -- and they also said they no longer have funding for some of the activities they were doing as part of that.

DR. JACKSON: But it wouldn’t seem to me that children would not have access to this, whether we voted yes or no, if it’s going to be administered through the CDC.

DR. SOBEL: Well, you could say the same thing about adults. I guess, based on what Dr. Epstein said -- maybe he should speak to that point.

DR. EPSTEIN: I was answering the question, what if we don't approve the pediatric dose? But there is an alternative, which is that we indicate in the labeling that, although approved for pediatric use, it isn’t based on clinical studies and that we recommend close monitoring, consideration of dose adjustments, retreatment, and so forth. I don't think it’s off the table to approve. We’re just asking what you think about the strength of the data from the modeling exercise.

DR. JACKSON: The question is really based on whether the animal studies and simulation modeling adequately supports the proposed dosing in pediatrics.

DR. EPSTEIN: And let me just make one more point. It’s not unprecedented for dosing recommendations to be made in the instance of animal studies, in the

absence of pediatric data, with the caveat that it has not been clinically established. That option is not vacated if you feel that, in fact, the modeling doesn’t support the dosing. We could approve it with a warning label.

DR. JACKSON: I think what some people are thinking is that the modeling might support it, but are the data strong enough that you have enough confidence in the modeling, I guess?

DR. BONILLA: I think, based on what we know about biologicals in general and the theoretical calculations this pediatric dosing is based on, the pediatric dosing is supported by the theoretical models. I think we can make provisions for postmarketing surveillance.

I don't know. I think we’re trying to cut it a little bit too finely here.

DR. SOBEL: I would like to echo Dr. Bonilla’s comment. I think the conjunction of the theoretical modeling here and what’s known about the physiological mechanism involved strongly argues for the use of this agent in treating botulism in children. But my position is that I think the absence of clinical data mandates vigorous, robust prospective collection of the data, recognizing that we’re dealing with a small number of pediatric cases -- on the average of five a year, to go by

the past few years -- and that the entire apparatus moving forward, if it is approved, or even if it’s not approved, needs to move forward with a determination to dedicate the resources to collecting this data prospectively. It’s essential.

MR. DUBIN: I want to support what Dr. Sobel just said. I think for those of with an arm in the game, so to speak, we have lots of data on recombinant factor usage, too, and every now and then I wake up and wonder -- well, the comment I make to my wife is, if I’m ever crawling around on the floor chasing cheese, get on the phone with Dr. José, because something’s wrong.

I think there’s always this concept that takes us back to the precautionary principle, which is, with great care, because people are using this.

So I would suggest, as you did, Dr. Sobel, that the critical point -- and I’m sorry, I’m ahead of question 4, but we seem to have gotten there -- the critical point is robust prospective surveillance that gives us the information we need. I think that’s critical.

I find, from our perspective, the recipients, three years is a little tight. You’re going to get a lot of retrospective, but you’re not going to get the prospective. I heard at the table today, I think from you, Dr. Sobel, that maybe it should be about how many people

we’re looking at, actually, rather than the amount of time we’re looking. I think we need to look for a better mechanism like that. And “robust” is the key word here, in my mind.

DR. JACKSON: Other comments?

DR. RHEE: I think we’re mixing a lot of questions in this particular question. The question is pretty simple. It just says, do the animal studies and the simulation models support the use in humans? Then we split it up. But I think it does for both. We just don't have good data for both. We know the reasons why we can’t get good data for both. But from the modeling and animal work, yes, it does.

DR. JACKSON: Anyone else?

(No response)

Then we will go ahead and vote on this question, 3b.

(The vote was taken.)

LCDR EMERY: The committee has voted. There are 12 yeses, there is one abstention, and there is one no. I’ll read the individual members.

Dr. Jackson, yes.

Mr. Corey Dubin, yes.

Dr. Sobel, yes.

Dr. Adler, yes.

Dr. Bonilla, yes.

Dr. Schexneider, yes.

Dr. Rhee, yes.

Dr. Stowell, yes.

Dr. Maguire, yes.

Dr. Kuzma, no

Dr. Demetriades, yes.

Dr. [Durkalski]-Mauldin, yes.

Dr. Gilcher, yes.

Dr. Kuehnert, abstain.

DR. JACKSON: Thank you.

DR. KUEHNERT: Do you want me to explain my abstention?

DR. JACKSON: Okay.

DR. KUEHNERT: I just think that if there's no data, it's impossible to form an opinion. I'd be happy to vote after there is postmarketing surveillance.

DR. JACKSON: All right, number 4: Based on the limitations of the safety database, FDA intends to require a postmarketing study to monitor safety of BAT. FDA proposes that Cangene utilize a registry to capture safety data on sporadic cases of botulism for a three-year period after licensure. Please comment whether such a registry would be adequate to add to the safety data for use of BAT in patients with botulism.

If I could clarify with the FDA, we're talking about on sporadic cases, not mass exposure, correct?

DR. EPSTEIN: Yes.

DR. SOBEL: A point of clarification. To me, a sporadic case means one lone case, without any epidemiologically associated cases. Yet an outbreak of two or three or five cases would not be considered a mass event. I assume that when we talk about sporadic cases here, we're really talking about sporadic and small outbreaks, as opposed to whatever a mass event is.

PARTICIPANT: I think so.

DR. JACKSON: Go ahead, Dr. Bonilla.

DR. BONILLA: All we've been told is that a registry is being developed and the structure and nature of the registry is under discussion between Cangene and the FDA. But we have no information about what information is to captured, how it's going to be organized, and so on. I don't know that we can answer as to the adequacy of the registry without knowing more about the registry.

DR. JACKSON: Matt, do you have a comment?

DR. KUEHNERT: Are you talking about the sporadic issue or the issue about the registry in general?

DR. JACKSON: I think the issue is whether a registry would be adequate to add to the safety data. He's saying, unless you know what the registry is going to ask

and what they are going --

DR. KUEHNERT: There’s a question about content and then there’s another question about how the registry is actually administered. Maybe Dr. Rao can give us some insight into what happened during the expanded access interval period. I think, before that period, the adverse reaction reports -- compliance was pretty poor. But if you position it to the physicians that if they want this product they will answer a follow-up on adverse reactions, you get a much better compliance rate.

So the question is how it’s going to go from here. The data will only be as good as how active your surveillance is.

DR. RAO: That’s right. Before H-BAT, we had very, very poor returns -- somewhere in the teens, 12 percent, 13 percent, something like that, for the return of paperwork. Now we don't actually say they have to complete this paperwork in order to get the product, but we send multiple letters. We had a person whose job it was to follow up. She had a timetable -- one week, make a phone call with these contents, the next week, do this. She escalated it all the way to sending a letter to the CEO of the hospital saying that under IND, they were required to return this paperwork, and when we released antitoxin to them, the cover letter said they had to complete it, that

sort of thing.

We have had much better success. It has gone up to 96 percent for two key forms that we need. It went from the teens to 96 percent just because we had this active follow-up, because of this person and because we could use the fact that it was IND to get that paperwork back.

We won’t have that anymore, this year.

DR. JACKSON: Let me get that right. You said you now have 96 percent compliance?

DR. RAO: For two specific forms. There are several forms. There are two specific ones, one monitoring for adverse events and one for outcomes. Those two forms -- 96 percent of them have been returned to us.

DR. KUEHNERT: Just to clarify about the active nature of the surveillance, do you require forms back even if there is no adverse reaction?

DR. RAO: That’s right. Every patient has to return these forms.

DR. KUEHNERT: That’s a very different sort of issue, where, even if there’s no reaction, they have to fax back or write back and say there’s no reaction. There you really get the picture of what’s going on, versus, well, just let us know if something bad happens, which is very different.

DR. JACKSON: But in this, number 4, it’s

proposing that Cangene do this as opposed to the CDC. You were saying that you were only getting 12 or 14 percent when you did it. So why would Cangene be able to do any better? It seems unlikely to me.

DR. RAO: That's true, and we're --

DR. JACKSON: And if we really want this data on children especially, it would seem that we would want to have some sort of postmarketing system that would be close to 100 percent, especially for children.

DR. GOLDING: The FDA's point of view is that we want to have a registry and we want the registry to be effective. My sense is that the other parties would like that as well. We have started negotiations. Our understanding is that the basic idea would be that the CDC is going to be contacted -- the CDC is the holder of the product -- the CDC would be contacted by a physician and the CDC would or would not release the product to the physician. The CDC would then contact Cangene, who is the holder of the license, and Cangene would then be responsible -- this is our view of it -- for collecting the data.

We have worked with many manufacturers under these circumstances. There are certain FDA rules and regulations that deal with this.

But we want to do this in a way that it's

negotiated with the company before the approval so that we have an optimal way of collecting the data. Are we there today? No. But we are involved in these negotiations, and that is the principle.

The committee has ideas of how the registry should be set up and what should be collected and they want to discuss that, that's fine. But the idea of the question was to determine whether, in the context of the approval of this product under the Animal Rule, this was a reasonable requirement -- and we think, for three years, we would have, on average, 50 patients a year -- whether that would be sufficient.

In an earlier discussion it was stated that we would look at the data after three years and then make a decision whether this registry needed to be extended or not.

DR. JACKSON: Given what Dr. Rao mentioned about the returns being so low, there would be no obligation by a clinician or a hospital to provide this to Cangene. There would be no legal observation to do so. Is that correct?

I just know that when we're told we need to report something to the CDC or our state health department, everybody takes that much more seriously than, can you report this to the manufacturer?

DR. SOBEL: I would like to make two comments.

One is specifically in response to the issue as to, concretely, how follow-up data would be collected, and the other one about the adequacy of a three-year monitoring period.

I think, in considering Dr. Rao's observations about collecting the follow-up information from the patients, there are two issues here: Who does it? And how much does it cost to do that?

I think that when it is the CDC Clinical Botulism Consultation Service that fulfills this function, in many cases, the same person who has actually performed the consultation with the emergency room or ICU physician, who has followed the case clinically, who has arranged the shipment of the antitoxin, who is a recognized expert on the topic and, of course, brings to bear all the influence of the public health system, including the state department of health and the hospital regulatory agencies -- I think there's a very strong case to be made for that same group following through the process and collecting that information, both in terms of the likelihood of collecting it and the handling of the data.

The second point is the cost. My understanding is that the Clinical Consultation Service is not funded at a baseline to do this. I think that any arrangement needs to consider the substantial person-power that it takes to

follow up on these cases -- multiple cases and multiple forms and a lot of persistence.

So that’s comment number one.

Comment number two, about the three-year period: It looks like antitoxin is being released at the rate of about 70 or 80 vials per year over the past two or three years, so another three years would mean about 200 to 250 more cases, almost all in adults. That would give probably a total of 500 cases since this program was initiated. Sample size calculations are required for determining what kind of certainty one would have about identifying adverse events of concern.

A three-year follow-up period would yield, based on the last three years of data, something like 15 children. I would be very concerned about the prospect of that number. When we think about children and we think about the small number and the fact that the one serious adverse event in this entire program was registered in a 10-year-old child, I think we need to plan at the outset for capturing a more robust universe of children receiving this product, to be able to really make meaningful determinations about its effectiveness and safety.

DR. JACKSON: Toby.

DR. SIMON: I was just going to point out, from the industry perspective, these types of postmarketing

studies are not terribly unusual. Companies frequently have this burden and accept it and take it as a part of doing business that they are required to obtain certain data. It varies, obviously, depending on the type of product and what the situation is.

I think, if I interpreted correctly, that CDC will not have funding to do this in the future, so Cangene will have to assume at least the cost of it. I don't know if it’s possible to subcontract to CDC. But it would be their burden to perform this.

In terms of the details, I think it is typical for the advisory committees to vote yes or no on the need for it, and once the need is established, FDA works with the company to create an acceptable postmarketing approval study, whether it be registry or some variation thereof.

So I think, from an industry perspective, this is not unusual or different. I think the comments have been heard, and FDA will almost certainly carry out, in terms of the pediatric cases, to get enough.

DR. JACKSON: I don't know if this is a vote. It asks us to comment as opposed to vote.

What about the option that the CDC would maintain a registry for just pediatrics and Cangene do the adults?

DR. SIMON: My understanding is that there’s no funding to do that. Is that correct?

DR. JACKSON: You are still going to be the ones distributing the product. You still have people involved. We're talking about seven or eight children over three years. Is that so onerous?

DR. RAO: Our service is basically me and a bunch of people in training. So it actually does turn out to be difficult, because the Epidemic Intelligence Service officers are the ones doing the consultations, releasing the antitoxin. They are traveling all around the world. They're in Kenya, whatever. They're not going to be able t make all these phone calls and send these emails. They are not around.

DR. JACKSON: Maybe I'm confused. You're not going to distribute the product at all and do this --

DR. RAO: No, no. We'll distribute the product. We just don't have the manpower to be able to have forms returned to us actively.

DR. JACKSON: But if we just restricted it to pediatrics, and we're talking about seven or eight over three years, two cases a year? You don't have the time to do that? I'm just asking.

DR. RAO: It's people in training who are -- it's tough to predict. Sometimes they are not even in the country. They're traveling all around.

DR. RHEE: The FDA doesn't have the money to do

it, and they want the company to do it. I think that's reasonable. It's usually done that way. Then the quality of the data that they get is basically up to them. They are going to have to report to the FDA with their registry to show the quality of their data. Then this is basically a burden that they take on. I think splitting it up between kids and adults is not necessarily a good idea. They already have a mechanism in place for letting them do it.

Now, if you go for three years and they have 15 kids, that's just because it's a rare event and they don't have that kind of event.

But I also can't imagine that the FDA ships out a product, they get it within hours, they infuse it right away, and the kid drops dead and they're not going to tell anybody about it. They are going to hear about it. I think anything could happen. We could have a hurricane in here. But I find that hard to believe, that that will occur, for such a rare event.

If it has to go out longer to get that kind of data -- what I'm looking for is, is it 1 out of 10, 1 out of 20, 1 out of 30? How often does this really work? Was it a fluke that that kid went into asystole? That's the kind of information that we're looking for. I'm not necessarily that interested I whether they get nausea and

urticaria and all this stuff.

DR. EPSTEIN: I just want to comment. There are existing reporting requirements for drugs in general which apply to plasma derivatives, including animal plasma derivatives. Manufacturers are obliged to investigate adverse event reports and they are obliged to provide periodic safety update reports to the FDA.

The distinction that we're making here is trying to move toward active surveillance, which yields denominators, which involves case investigation and reporting -- what exactly were the circumstances? For example, was there premedication? We heard that in the CDC database they generally didn't know if there was premedication.

I think the thrust of this question was really, if not a registry, then what? In other words, we hear loudly and clearly that there's a desire to have a significant postmarket surveillance. FDA thinks the same thing. That's what you have heard from us. I think the essence of the question is -- there's a menu of options for what can happen postmarketing, but they are quite limited in this instance. Nobody is going to do an additional controlled trial. If you could have done that, you would have done it in the first place, premarketing. Then you can talk about structured surveillance, which is this

registry idea, where you get denominators, you get complete case investigation, you get outcome measures, and you have better reporting of the actual conditions of the patient. Or you can simply have routine passive surveillance, where, yes, there is a requirement to report serious adverse events to the FDA -- and certainly unexpected serious adverse events actually are subject to rapid reporting -- but the problem there is that it’s all passive and it’s unstructured. You get what you get.

This is really what we’re getting at. I think we’re heard that, particularly for pediatrics, three-year surveillance might not be enough. I think you have heard that, since the CDC is not prepared under its current funding mechanism to maintain, in effect, a registry, FDA wants to negotiate this with the sponsor.

DR. JACKSON: I always think of passive registries, and what’s really different this time is that CDC will know exactly who got every single dose and you will give that information to the company. Therefore, unlike most registries where they don't know necessarily who is getting all these drugs, they will know that. If they have it internally set up that they will investigate and actively get back to the clinicians who you gave the product to, we would be much more likely to get this data, if it really is active follow-up. And they can do it

because they will know exactly who got it.

DR. SOBEL: I would like to respond to your comment and also the last comment made. Indeed, what is unique about this situation is that the universe of recipients of this product is and will be known.

What is also unique about it -- and this is different from all other biologics, as far as I know -- is that there is already a clinical consultative relationship between Dr. Rao and her staff and the clinicians at the hospital who are treating that. That represents an opportunity for continuity and for effectiveness.

The resources that we're talking about, if I understand correctly -- we're talking about basically one full-time person, right? This is not building a laboratory facility. It's one midlevel trained person who can do this.

I would point out that one of the unique aspects of this situation is, for a calculable cost, leveraging all of these advantages and the substantial up-front investment of professional time in performing the clinical consultancy and the arrangement of the shipment of the antitoxin, for the public health infrastructure to follow through and complete this data collection.

DR. KUEHNERT: I agree with those comments. I think, given the infrastructure already existing, it would

be a shame to waste that.

But I think, no matter what happens, the important thing is the active nature of the surveillance. In other words, it's not how the company appreciates the importance. It's really about the clinicians. I think if a clinician has to fill out a form and say there was no adverse reaction and sign off on that, they will be reluctant if there was one. If they are asked to just voluntarily do it, they'll think, well, maybe it wasn't serious enough for me to report it. It's a whole different story.

I think that is a very key thing for FDA to consider in terms of what they require in the registry.

DR. JACKSON: Number 5: The Animal Rule requires postmarketing studies to monitor safety and efficacy of products approved under the rule when such studies become ethical and feasible. To address this requirement, the Agency proposes that Cangene reactivate the previously established registry, as indicated in question 4, to capture safety and efficacy data in any mass exposure scenario. Please comment whether such a registry would be adequate, one, to monitor the effectiveness of the recommended human dose in cases of botulism, and two, to add to the safety data.

Comments on that? Dr. Bonilla.

DR. BONILLA: Presumably, in this kind of scenario with mass casualties, there will be perhaps individuals who could be treated in time and other individuals who could not, who, in fact, had botulism, but would never be given an opportunity to receive H-BAT. That would perhaps really give you better data regarding efficacy than any other kind of circumstance.

But then the question becomes, how does one enforce the capture the data for cases in which H-BAT was never administered?

DR. JACKSON: The other thing is, unless you actually know what the exposure was, it’s hard to know the efficacy. You’ll know ultimately the deaths and that sort of thing. But it’s going to be very dependent on the exposure, the amount of toxin in the blood that they ultimately get. If you don't know that, if you don't have a test for that and you can’t measure that, then it’s sort of hard to measure the efficacy, other than saying, well, we gave it and it didn’t work, so it must have been a high dose, or we don't know whether we gave enough, or it was inactive. It’s hard to know.

DR. SIMON: It’s an important point. I think they can do the best that they can. In commenting, I wouldn’t say it would be adequate, but it would be the best you could do.

I think the point that was made by the FDA about the Animal Rule says when possible and when ethical. To the extent possible, of course, one would want that data. The company, I assume, would be willing to do that. But we would just have to take into account that in a mass casualty situation, there are going to be limitations as to the practicality, for some of the reasons you have already suggested -- as well as everybody rushing around to try to save lives.

DR. JACKSON: Maybe Dr. Kovacs can comment. Is it likely, with a mass exposure, whether it’s natural or a bioterrorist, that you will be able to measure the source and get some idea of the levels? Is that likely?

DR. KOVACS: If I understand your question correctly, you’re asking, is it likely that we will be able to determine the amount of toxin?

DR. JACKSON: Right, the exposure.

DR. KOVACS: I think the best we could probably do is epidemiological studies to determine where it was dispersed, but not so much how much was dispersed.

DR. JACKSON: Clearly if it’s a food type of exposure, I would think you would probably have access to the food at some point and could determine that.

DR. KOVACS: You could probably back-calculate how much material was in that source of contaminant.

DR. JACKSON: Dr. Rao, you wanted to comment?

DR. RAO: Yes. I was just going to say that even in food -- right now with foodborne outbreaks, we'll have some people who are much more strongly affected than others because the toxin is not uniformly distributed within that food. It would still be difficult. It depends on how much they ate. It depends on how uniformly distributed it was.

DR. SCHEXNEIDER: One of the reasons that we're developing this drug is to address a bioterrorist attack. Certainly, as folks have said, we're not going to know how much of the toxin is there. We're not going to know how much of a dose people ingest. But we do the best we can. Certainly if we acquire a lot of data, we just sort through it, shake it out, and derive whatever lessons we can from it. So I would certainly encourage us to gather whatever data we can.

DR. STOWELL: It seems to me that measuring levels of the toxin in the blood serum or stool or whatever the samples are would be the way to go in terms of determining -- I don't think there's any way to predict on the basis of how much toxin there is in the sugar packets and whether they used one or two teaspoons or any of the rest of it, to figure it out.

I would also say this is true of every single piece of human data that we have so far. Nobody got a

standard dose of any of the things that we have looked at, because none of these were experimental exposures. This data that we're going to get post-licensing is going to be no different from what we got pre-licensing.

DR. MAGUIRE: I just wonder if data collection and planning is part of the whole procedure for preparation for emergencies. In other words, could that be part of the emergency response planning, protocols for data collection and evaluation?

DR. KUEHNERT: I think, essentially, when you are talking about a mass casualty scenario, it's a battlefield situation. I think the question is whether it would be adequate, when, really, I think the question should be, would it be helpful to get what you can? I'm just echoing the other comments. I think we have to be careful of what we require in that scenario, because it probably won't be feasible. Rather, we should just try to get what we can in that sort of situation -- be prepared, have questions on the ready, but realize that in that situation it just may not be possible to get any kind of organized information.

DR. JACKSON: Anyone else?

(No response)

The next one is to add to the safety data. The same types of comments?

(No response)

Okay, then we'll move to number 6: Please comment on FDA's proposal that Cangene should commit to a postmarket study to determine blood levels of botulism antitoxin heptavalent, A, B, C, D, E, F, G, equine, after therapeutic dosing in children in order to validate the dosing recommendations in the absence of a pediatric PK study.

I think we've commented quite a bit on this already. It's slightly different. This is not a registry we're talking about here, but a postmarket study.

DR. SIMON: I think here also it's a practicality issue. Would it be appropriate to ask the company to respond on this one?

DR. JACKSON: Does Cangene want to comment on that or not?

DR. HALL: We can certainly do such a study if required. It is difficult to consent, through their parents, into these studies and get samples. However, we do have the adult model that we can use as a basis to analyze any sampling that we do get.

DR. JACKSON: I would think, if a child was actually diagnosed with botulinum toxicity and treated, getting a parent to agree to get some specimens -- I do a lot of pediatric clinical trials. I think in that context it would be very feasible to do that. I think they would

allow that.

I think the bigger issue is that there are just not going to be many cases.

DR. EPSTEIN: I wonder if we could ask a speaker from Cangene to comment on what the barriers were to doing a pediatric PK study in healthy children. Was it attempted? Could it be done? What were the barriers?

DR. HALL: No, we did not undertake such a study. Our feedback has been that it’s unlikely that we would be able to do such a study in healthy children due to ethics.

DR. SIMON: That has been our experience also, that ethics committees are very reluctant to permit these kinds of studies in healthy children.

DR. JACKSON: In my experience, the IRB and the regulations, you have to show benefit for a healthy child to undergo an intervention like this. They have to have a benefit. There would be no benefit here, really, for healthy children.

DR. EPSTEIN: If I could clarify, the standard for an IND is that you have to preclude unreasonable risk. You don't have to have a study where you’re balancing a potential benefit against harms.

I think the issue here is that the product is equine and we know that there is a potential -- quite real -- for allergic reactions, as well as immunogenicity,

and you are going to get antibodies to horse protein.

I think the question is whether in a pediatric group that’s an unreasonable risk. That would be the regulatory issue.

DR. JACKSON: You’re right, but with the data we have seen, I don't think any IRB would think that there’s not significant risk here. I don't think you could do it.

Comments in terms of a postmarketing study, other than what we have been talking about -- getting data through a registry -- in terms of literally trying to get some blood samples from a child who has been hospitalized and treated, to be able to, let’s say, measure toxin levels or antitoxin levels? Those sorts of things, to me, would seem feasible. You could do this with specimens that have already been -- hospitals keep these typically for ten days, whether it’s in chemistry or hematology or blood bank or whatever. So there could be specimens there that you could get to get that information, which you wouldn’t get from your registry. There may be some good data you could get that way.

DR. KUZMA: I was just going to say it seems like it would be a good thing to do. I agree. If we were to vote on this, I would vote yes.

DR. SIMON: But just in terms of practicality, let’s say the child is in a small hospital on the Arizona

border and not in Johns Hopkins, where they don't do clinical research. I think the practicality of consenting and arranging it and so forth is rather daunting, which is why I suggested that the company comment. I think it would be good if we could get this kind of data, but I think it’s just very difficult.

DR. JACKSON: I would agree that it would be tough to do this prospectively -- at the time CDC is notified, to try to do this ahead of time. But there will be samples that have already been collected as just part of the child’s stay. These are already collected. They are just sitting in the lab somewhere. One could easily, I would think, get permission from parents to get those specimens and test them for the antitoxin levels to look at the dosing issues. All specimens on a patient when they are collected in the hospital have a date and a time when they are collected. You could get some data.

I don't know if Dr. Staschen would have any comment on that for his modeling, but I would think those types of specimens could give you some data about the dosing.

DR. STASCHEN: Exactly. The idea is not to prepare a full PK study. Occasionally, if available, additional samples are taken and just could be sent to us so that we can look at the dose and the concentration that

was achieved.

DR. JACKSON: Any other comments on this topic?

Jay, do you have any other issues that you want us to address or clarify?

DR. EPSTEIN: I just want to thank the committee for a very helpful discussion. I appreciate all the attention to all these points of concern. I hope everyone has a safe trip back.

DR. JACKSON: Toby.

DR. SIMON: I just want to make a closing comment. Hopefully it won't be taken politically. I think it's just wonderful to see the cooperation between the private sector and the public sector here, and the involvement with FDA. I think it's just a great example of what we can accomplish when we work together.

MR. DUBIN: A long way from where we were 20 years ago. I want to endorse what you said, Toby. It was us being on different sides at one time, and not so much anymore. I appreciate it. I think this is a good example. I said that to Dr. Epstein earlier. From A-Plus's side, we're pretty pleased at what we see from the users.

DR. JACKSON: Is there anything else, Bryan, that I need to say that I have forgotten?

Thank you all very much for taking your time, everyone in the room. I know it's a lot of time to come.

It has been a very interesting topic.

(Whereupon, at 4:22 p.m., the meeting was adjourned.)