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MEDICAL DEVICES ADVISORY COMMITTEE

GENERAL HOSPITAL AND PERSONAL USE DEVICES PANEL

THIRTY-SIXTH MEETING

TUESDAY, SEPTEMBER 27, 2005

PRESENT:

- |                                  |                         |
|----------------------------------|-------------------------|
| CHARLES E. EDMISTON, Jr., Ph.D.  | CHAIRMAN                |
| LT. SCOTT COLBURN, BSN, RN       | EXECUTIVE SECRETARY     |
| MATTHEW J. ARDUINO, D.Phil.      | VOTING MEMBER           |
| RICHARD O. BUTCHER, M.D.         | VOTING MEMBER           |
| RICHARD L. EVANS, LTC, AN, MS    | VOTING MEMBER           |
| JAMES GORDON, MD, FACP           | VOTING MEMBER           |
| LESLIE C. GRAMMER, PH.D.         | VOTING MEMBER           |
| SEVEN J. HAINES, MD              | VOTING MEMBER           |
| WILLIAM R. JARVIS, MD            | VOTING MEMBER           |
| DEAN KEVIN LURIE, MD, FACS       | VOTING MEMBER           |
| SUZETTE A. PRIOLA, PHD           | VOTING MEMBER           |
| MANGAIYARAKARASI SANTHIRAJ, MPH  | VOTING MEMBER           |
| GLENN C. TELLING, PH.D.          | VOTING MEMBER           |
| LAWRENCE B. SCHONBERGER, MD, MPH | VOTING MEMBER           |
| ROBERT COFFEY, MD                | INDUSTRY REPRESENTATIVE |
| ELIZABETH HOWE                   | CONSUMER REPRESENTATIVE |
| CHIU S. LIN, Ph.D.               | FDA                     |

**This transcript has not  
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P-R-O-C-E-E-D-I-N-G-S

(8:02 a.m.)

1  
2  
3 CHAIRMAN EDMISTON: Good morning. I'd  
4 like to call this 36th meeting of the General Hospital  
5 and Personal Use Device Panel to order. My name is  
6 Charles Edmiston. I'm a Professor of Surgery of the  
7 Medical College of Wisconsin. I'll be chairing  
8 today's meeting. I would like to request everyone in  
9 attendance at this meeting to sign in on a sheet  
10 that's available at the table on the outside of the  
11 door.

12 I note for the record that the voting  
13 members present constitute a quorum as required by 21  
14 CFR Part 14. At this time, I would like to ask the  
15 members of the panel, starting on my far left, to  
16 introduce themselves, state his or her position and  
17 title and their status on the panel.

18 DR. LIN: My name is Chiu Lin. I'm the  
19 Director of Division of General Hospital Infection  
20 Control and Dental Devices.

21 DR. TELLING: I'm Glenn Telling. I'm as  
22 Associate Professor of Microbiology and Immunology.

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1 It's a Center of Aging at the University of Kentucky.

2 DR. HAINES: Steve Haines. I'm Professor  
3 and Head of the Department of Neurosurgery at the  
4 University of Minnesota.

5 DR. GORDON: Jim Gordon. I do Infectious  
6 Diseases. I'm as Assistant Professor at the Medicine  
7 at Wayne State University.

8 DR. JARVIS: Bill Jarvis, President of  
9 Jason and Jarvis, Associates in Hilton Head, South  
10 Carolina.

11 DR. GRAMMER: Leslie Grammer, I'm a  
12 Professor of Medicine at Northwestern University,  
13 Feinberg School of Medicine in Chicago.

14 LT. COLBURN: Scott Colburn, I'm the  
15 Executive Secretary to the General Hospital and  
16 Personal Use Devices Panel.

17 DR. BUTCHER: I'm Richard Butcher. I'm in  
18 family practice in San Diego.

19 DR. ARDUINO: Matt Arduino. I'm the lead  
20 microbiologist in the Epidemiology and Laboratory  
21 Branch, Division of Health Care Quality Promotion at  
22 CDC.

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1 DR. SCHONBERGER: I'm Dr. Lawrence  
2 Schonberger and I'm an Assistant Director for Public  
3 Health in the Division of Viral and Reckettsial  
4 Diseases at CDC.

5 MR. EVANS: Good morning. I'm Richard  
6 Evans. I'm a Registered Nurse and Clinical Nurse  
7 Specialist in Medical/surgical Nursing, also active  
8 duty Army Nurse Corps Officer.

9 DR. PRIOLA: Sue Priola. I'm a Senior  
10 Investigator with the National Institutes of Health.

11 DR. LURIE: Dr. Kevin Lurie, General and  
12 Vascular Surgery here in Washington, DC.

13 MS. SANHIRAJ: Manga Sanhiraj, infection  
14 control Practitioner, Epidemiologist at Hines VA  
15 Hospital, Chicago.

16 MS. HOWE: Betsy Howe, President of Non-  
17 Profit Consultants, a consulting firm for National  
18 Voluntary Health Organizations, Seattle, Washington.  
19 I am serving as the consumer representative.

20 DR. COFFEY: Robert Coffey, Medical  
21 Director in the Neurological Division of Medtronic,  
22 Inc. and I'm the industry representative.

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1 CHAIRMAN EDMISTON: Thank you. Lt. Scott  
2 Colburn, the Executive Secretary would like to make  
3 some introductory comments. Lt. Colburn.

4 LT. COLBURN: Before I begin, I'd like to  
5 ask that all cell phones and pagers be turned off or  
6 placed into the silent ring mode, so they do not  
7 interrupt the business of this meeting.

8 The FDA seeks communication with industry  
9 and the clinical community in a number of different  
10 ways. First, FDA welcomes and encourages pre-meetings  
11 with sponsors prior to all IDE and PMA submissions.  
12 This affords the sponsor an opportunity to discuss  
13 issues that could impact the review process.

14 Second, the FDA communicates through the  
15 use of guidance documents. Toward this end, FDA  
16 develops two types of guidance documents for  
17 manufacturers to follow when submitting a pre-market  
18 application. One type is simply a summary of the  
19 information that has historically been requested on  
20 devices that are well-understood in order to determine  
21 substantial equivalents. The second type of guidance  
22 document is one that develops as we learn about new

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1 technology. FDA welcomes and encourages the panel and  
2 industry to provide comments concerning our guidance  
3 documents.

4 At this time, I'd like to read into the  
5 record the ethics conflict of interest disclosure  
6 statement as required. "The Food and Drug  
7 Administration is convening today's meeting of the  
8 General Hospital Use Devices Panel of the Medical  
9 Device Advisory Committee under the authority of the  
10 Federal Advisory Committee Act of 1972. With the  
11 exception of the industry representative, all members  
12 and consultants of the panel are special government  
13 employees or SGEs or regular federal employees from  
14 other agencies and are subject to federal conflict of  
15 interest laws and regulations.

16 The following information on the status of  
17 this panel's compliance with federal ethics and  
18 conflict of interest laws covered by but not limited  
19 to those found at 18 USC 208 and 21 USC 355 number 4,  
20 is being provided to participants in today's meeting  
21 and to the public. FDA has determined that members  
22 and consultants of this panel are in compliance with

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1 federal ethics and conflict of interest laws. Under  
2 18 United States Code Section 208, Congress has  
3 authorized FDA to grant waivers to special government  
4 employees who have limited financial conflicts when it  
5 is determined that the agency's need for a particular  
6 individual's services outweighs his or her potential  
7 financial conflict of interest. Members and  
8 consultants of this panel who are special government  
9 employees at today's meeting have been screened for  
10 potential financial conflicts of interest of their own  
11 as well as those imputed to them including those of  
12 their employer, spouse or minor child related to the  
13 discussions of today's meeting.

14 These interests may include investments,  
15 consulting, expert witness testimony, contracts,  
16 grants, CRADAs, teaching, speaking, writing, patents  
17 and royalties and primary employment. Today's agenda  
18 involves a discussion regarding general issues related  
19 to a model to be used for validation testing to  
20 support a claim of decontamination of potentially  
21 transmissible spongiform encephalopathy or TSE  
22 contaminated surgical instruments." Based on the

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1 agenda for today's meetings and all financial  
2 interests reported by the panel members and  
3 consultants, no conflict of interest waivers have been  
4 issued in connection with this meeting. Dr. Robert  
5 Coffey is serving as the industry representative  
6 acting on behalf of all related industry and is  
7 employed by Medtronic, Incorporated.

8 Mr. Alan Hilderly, a senior medical device  
9 specialist for the Medicines and Healthcare Products  
10 regulatory agency of the United Kingdom is a guest  
11 speaker today. We would like to remind members and  
12 consultants that if the discussions involve any other  
13 products or firms not already on the agenda for which  
14 an FDA participant has a personal or imputed financial  
15 interest, the participants need to exclude themselves  
16 from such involvement and their exclusion will be  
17 noted for the record.

18 FDA encourages all other participants to  
19 advise the panel of any financial relationships that  
20 you may have with any firms at issue. This conflict  
21 of interest will be available for review at the  
22 registration table. Thank you.

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1           The first item on our agenda is a  
2 presentation by Dr. Sousan Altaie. She will be  
3 discussing the challenges and opportunities in the  
4 critical path to new medical devices. Dr. Altaie.

5           DR. ALTAIE: Good morning. I'm Sousan  
6 Altaie, the Scientific Policy Advisor OIVD and I am  
7 the liaison for critical path initiatives in CDRH.  
8 Next slide, please.

9           Today I'm going to talk to you about the  
10 critical path initiative at the FDA and why is the FDA  
11 interested in critical path and what are the critical  
12 path tools. And then we're going to talk about the  
13 medical devices areas of interest under critical path  
14 and we are then going to talk about the actual  
15 projects going on at the center and then I will give  
16 you a chance to get involved if you feel like you can  
17 help.

18           Critical path is a serious attempt to make  
19 product development more predictable and less costly.

20           And when you think of critical path, you should think  
21 of the life cycle of the product development from the  
22 basic research to the prototype being pre-clinical and

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1 clinical development then finally, application and  
2 approval of the device. Well, critical path covers  
3 the journey through the prototyping all the way to  
4 approval and does not deal with the basic research.  
5 Next slide, please.

6 You might wonder why the FDA is interested  
7 in the critical path, because we realize the  
8 significant benefit of bringing innovative products to  
9 the public faster. Because we have a unique  
10 perspective on product development. We see the  
11 successes, failures and the missed opportunities and  
12 because it will help us develop guidance and standards  
13 for faster innovations. And next slide, please.

14 We work together with the industry,  
15 academia and patient care advocates to modernize,  
16 develop and disseminate solutions, these are the tools  
17 we are going to talk about on the critical path, to  
18 address scientific hurdles in device development.  
19 Next slide, please.

20 Now, what are critical path tools?  
21 Critical path tools are the methods and the techniques  
22 used in three regulatory dimensions. These dimensions

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1 are an assessment of safety, the tools predict if a  
2 potential product will be harmful. A proof of  
3 advocacy, it took to determine if a potential product  
4 will have medical benefit. And under  
5 industrialization, the tools help in manufacturing the  
6 products with consistent quality. Next slide, please.

7 Some critical path tools at CDRH we think  
8 of biomarkers, Bayesian statistics, animal models of  
9 biomarkers, critical trials design -- clinical trial  
10 design, computer simulation, quality system protocols,  
11 post-market reporting, and you're welcome to add to  
12 our list of critical path tools. Next slide, please.

13 If you look at the devices that we  
14 regulate at CDRH they range anywhere from a bandaid to  
15 a stethoscope to hand-held glucose monitors, to heart  
16 valves and scents and MIS and PET scans. So there are  
17 a lot of opportunities where we could foster  
18 innovation and help products getting on the market in  
19 a vast range of devices. Next slide, please.

20 However, our critical path is in nature  
21 different than the critical path in drug development.  
22 That is because our devices are complex components.

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1 We deal with bio-compatibility. We have durable  
2 equipments, not short-life devices and we deal with  
3 the rapid product cycles that are totally being  
4 improved and changed every time you turn around. And  
5 device malfunctions are an important problem that we  
6 deal with and user errors. And we approve devices  
7 based on bench and clinical studies versus drugs that  
8 they only base their approvals on the clinical  
9 studies. And our regulations are totally different.  
10 We deal with quality system regs and ISO 9000 as --  
11 versus the GMPs where the drugs are regulated under.  
12 Next slide, please.

13 So what are the medical devices of  
14 interest in CDRH? Under device safety tools, we think  
15 of bio-compatibility, data bases, effects of products  
16 on diseased or injured tissues. Next slide.

17 Under device effectiveness tools, we think  
18 of surrogate implants for cardiovascular trials and  
19 computer simulation modeling for implanted devices.  
20 Next slide, please.

21 Under the device mass manufacture or  
22 utilization tools we think of practice guidelines for

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1 follow up of implanted devices, validated training  
2 tools for devices with a known learning curve and for  
3 validation of biomarkers we're looking at -- we're  
4 looking to generate blood panels to assess sensitivity  
5 and specificity. For peripheral vascular scents we  
6 are working with the Stanford University to develop  
7 computer models of human physiology to test and  
8 predict values and that is before going into animal  
9 and human studies. For intrapartum fetal diagnostic  
10 devices we are working within NIH to develop a clear  
11 regulatory path with consensus from outside the  
12 community.

13 We are collaborating with NIH on  
14 pharmacokinetics and image guided interventions. We are  
15 working with CDC and Johns Hopkins to develop a well-  
16 defined serum panel to test sensitivity and  
17 specificity of the new hepatitis assays. We're  
18 working on pathways for statistical validation of  
19 surrogate markers, especially in the area of  
20 cardiovascular devices. Next slide, please.

21 We are working with the medical specialty  
22 organizations to develop practice guidelines for

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1 appropriate monitoring of permanently implanted  
2 devices and finally, we are determining the extent of  
3 near toxicity testing for neuro-tissue contacting  
4 materials.

5 So if you are thinking about getting  
6 involved with critical path, you actually can do two  
7 things. You can send comments to the docket on the  
8 FDA critical path White Paper and identify areas that  
9 benefit from research and development of critical path  
10 evaluation tools. And you also can add to the  
11 National Critical Path Opportunities List that we are  
12 compiling at the FDA and good news, I saw the first  
13 draft, so its coming along. Next slide, please.

14 And these are actually websites where you  
15 could go see the paper, the White Paper of the  
16 Critical Path Initiative and where you could actually  
17 see the docket as well, give us all the comments,  
18 suggest new tools and tell us how we can help to put  
19 devices more on the market more faster. Next slide,  
20 please.

21 I'd like to leave you with this thought;  
22 that at CDRH we believe that insuring the health of

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1 the public through the product life cycle is  
2 everyone's business so I suggest you get involved.  
3 With that, is there any questions?

4 LT. COLBURN: Are there any questions for  
5 Dr. Altaie?

6 DR. ALTAIE: Yes.

7 DR. SCHONBERGER: I wonder if you could  
8 clarify how this relates to the TSE issue.

9 DR. ALTAIE: I'm sorry, what does TSE  
10 stand for?

11 DR. SCHONBERGER: The transmissible  
12 spongiform encephalopathy problem. Have you run into  
13 difficulty with this critical path as regards to the  
14 TSE or prions or CJD?

15 DR. ALTAIE: We are looking for techniques  
16 and methodologies and I described what the tools are  
17 thought of when we talk about critical path and I  
18 actually have not seen a project that was put forth  
19 under the entire list that I saw. So that is a great  
20 opportunity for you to get involved. If you think  
21 there are tools and possibilities to address the TSE,  
22 all power to you, suggest it to us. I saw the first

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1 draft of the critical path projects that was put  
2 forward and that wasn't one of them. So obviously  
3 nobody's thinking about it.

4 DR. SCHONBERGER: So at this point it has  
5 not been a problem for you; is that right?

6 DR. ALTAIE: No. Obviously, I don't know  
7 what has been coming through for approvals and I guess  
8 this is the first one decontamination; is that  
9 correct? Dr. Chiu, can you answer that? Dr. Chiu  
10 will try to address that.

11 LT. COLBURN: Dr. Chiu Lin.

12 DR. LIN: If I may, the answer to your  
13 question, as Dr. Altaie pointed out, this critical  
14 path is FDA's new way or more better the thinking how  
15 we should approve a product and we are seriously  
16 thinking how, you know, the product approval process  
17 should be captures with new science and new  
18 technology. So if TSE panel meeting as we are going  
19 to discuss probably some time today, essentially that  
20 a new way of thinking for some product that can  
21 contaminate surgical instrument, how we should to  
22 about to approve those product. That's probably in

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1 line with what the Doctor Sousan Altaie just  
2 mentioned.

3 DR. ALTAIE: All right, so I actually  
4 think you just identified an area in critical path  
5 where you could help, so all power to you. Any other  
6 questions? All right, thank you.

7 LT. COLBURN: Thank you, Dr. Altaie. At  
8 this time I wanted to indicate for the record that Dr.  
9 David Gaylor, who is listed as a panel participant was  
10 unable to attend today due to a personal circumstance.

11 And at this time, I'd like to turn the panel meeting  
12 back over to our Chair, Dr. Edmiston.

13 CHAIRMAN EDMISTON: Dr. Chiu Lin, Director  
14 of the Division of Anesthesiology, General Hospital  
15 Infection Control and Dental Devices would like to  
16 give a brief Division update. Dr. Lin.

17 DR. LIN: Good morning. As I pointed out  
18 earlier, my name is Chiu Lin. I'm the Director of  
19 Division of Anesthesiology General Hospital Infection  
20 Control and Dental Devices. Before I begin I wanted  
21 to take this opportunity to thank the panel member to  
22 come to assist the agency to address this very

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1 important scientific issue that confronts the agency  
2 and I appreciate very much for your time.

3 I thought I want to take a few minutes of  
4 your time to sort of introduce to you our divisions  
5 and to sort of let you know where we stand in the  
6 CDRH's organizations. Next please.

7 As you know CDRH probably during your  
8 training you probably already know. CDRH composed of  
9 six office and one of the office, the Office of Device  
10 Evaluation is the largest office in CDRH organization.

11 The Office of Device Evaluation, ODE, the primary  
12 responsibility of ODE is involved to approve any new  
13 product and new medical device that to be marketed in  
14 the United States, that is our job. Next.

15 The Office of Device as an organization  
16 also is divided into five divisions and this division,  
17 five divisions divides according to product lines. So  
18 and the Division of -- as I mentioned, I'm in the  
19 Division of Anesthesiology, General Hospital Infection  
20 Control and Dental Device. We have four product lines  
21 that come under our responsibility. Next.

22 So in terms of management, I have a Deputy

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1 Director. It's Dr. Ginette Michaud, who is right  
2 here. Can you stand up? She's the Medical Officer  
3 and she very much assist me in terms of medical --  
4 issue related to medical affairs. And then as I  
5 mentioned, the Division has four product lines and  
6 that's how we organize and divide into four branches.  
7 You have Anesthesiology is headed by Ann Graham and  
8 we have Dental Device headed by Susan Runner. We have  
9 General Hospital Device, it's headed by Anthony Watson  
10 and we have Infection Control Device branch is headed  
11 by Dr. Sheila Murphy, who is going to speak right  
12 after me.

13 I would sort of give you some overall of  
14 how in terms of advisory panel is concerned that our  
15 division as three advisory panel. One is  
16 anesthesiology and respiratory or therapy device panel  
17 and the second one is a dental device panel and the  
18 third one is this panel, it's a General Hospital and  
19 Personal Use Device Panel, which is shared by two  
20 branches. One is for General Hospital Device Branch  
21 and one is Infection Control Device Branch.

22 And two months ago, we just had a panel

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1 meeting that very much devote to general hospital  
2 device issues. So today's panel meeting essentially  
3 is going to be devoted to infection control device  
4 issues. Thank you.

5 I would be happy to entertain any question  
6 if anybody has any questions.

7 CHAIRMAN EDMISTON: Thank you, Dr. Lin.  
8 We will now proceed with the FDA's presentations of  
9 the panel topics. We have four presenters. The first  
10 speaker will be Dr. Sheila Murphy, Chief of the  
11 Infectious Disease, Infection Control Devices Branch.  
12 Dr. Murphy.

13 DR. MURPHY: Good morning, members of the  
14 panel. Thank you very much for joining us today and  
15 providing us with your advice. May I have -- this  
16 morning, we are seeking your advice for general  
17 scientific issues related to the topic of  
18 transmissible spongiform encephalopathy and in  
19 particular the transmissible aspects of TSEs. Next  
20 slide, please.

21 I'm Dr. Sheila Murphy. I am the Branch  
22 Chief for the Infection Control Devices Branch. My

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1 background is infectious diseases and hospital  
2 infection control. Next.

3 This morning, we are asking you to address  
4 the scientific issues surrounding the evaluation of  
5 products or processes intended to reduce the bio-  
6 burden of the Jakob-Creutzfeldt transmissible agent on  
7 contaminated surgical instruments. Next.

8 In July of 2003, the DAGID, the Division  
9 of Anesthesiology General Hospital Infection Control  
10 and Dental Devices asked the Transmissible Spongiform  
11 Encephalopathy's Advisory Committee known as TSEAC to  
12 address the issue of reprocessing medical devices  
13 contaminated or potentially contaminated by TSE  
14 agents. The questions on instrument decontamination  
15 asked of TSEAC were general and they received general  
16 responses. TSEAC pointed out to us that little of the  
17 experimental literature on TSE inactivation is  
18 directly applicable to hospital settings. TSEAC  
19 stated that there was no threshold below which  
20 exposure to a TSE agent should be considered to be  
21 safe.

22 TSEAC also stated that use of existing

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1 methods cannot insure that complete removal of TSE  
2 agents from all materials under all circumstances.  
3 DAGID believes that it now needs more guidance on the  
4 issues of TSE contamination of surgical instruments.  
5 The number of scientific articles published addressing  
6 the reduction or removal of TSE from instrument  
7 proxies is increasing in the scientific literature.  
8 Public interest in and concern about variant CJD  
9 disease and its potential for causing infections in  
10 the United States is also increasing.

11 DAGID therefore, believes that each should  
12 prepare for the possibility that products or processes  
13 intended to reduce TSE infectivity on surgical  
14 instruments will be submitted to FDA for pre-market  
15 evaluation. This morning you are going to hear four  
16 presentations from FDA. Dr. Elaine Mayhall, a  
17 reviewer in the Infection Control Devices Branch, will  
18 be giving you a general introduction to transmissible  
19 spongiform encephalopathies. I am going to discuss  
20 with you some of the issues related to evaluating the  
21 in vivo models of TSE transmission.

22 Dr. Estelle Russek-Cohen from our Office

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1 of Surveillance and Biometrics, will be discussing the  
2 statistical aspects of evaluating the results of such  
3 studies and Ronald Brown from the Office of Science  
4 and Engineering Laboratories, will be presenting a  
5 risk analysis addressing the risk of actual  
6 transmission of Creutzfeldt-Jakob disease in the  
7 United States, not in the UK but in the United States  
8 with the parameters in force here at the present time.

9 Next.

10 We also have a guest speaker, Mr. Allan  
11 Hilderley, who is a senior medical device specialist  
12 from the Medicines and Health Care Products'  
13 regulatory agency, the Device Section, in the United  
14 Kingdom. This is our sister agency in the United  
15 Kingdom and he will be discussing these issues from  
16 the UK point of view. Next.

17 We ask the panel to address a number of  
18 questions today. We'd like to review these with you  
19 before we start so that you can be thinking about them  
20 during our presentations. Our first question for you  
21 is, assuming that a product sponsor seeks a claim for  
22 reducing TSE infectivity on stainless steel

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1 instruments, is it reasonable for such an indication  
2 to be validated using animal studies of TSE  
3 transmission? Please discuss this.

4 Discuss the relevance of various design  
5 features of such validation studies for drawing  
6 conclusions. Of the three study end points cited in  
7 the literature, which are log reduction in  
8 infectivity, mean incubation time, and survival as  
9 median survival and as percent survival, which, if  
10 any, may be adequate for the validation of a reducing  
11 TSE infectivity indication? Should demonstration of a  
12 particular level of reduction of TSE infectivity in  
13 one or more end point be expected in order to support  
14 an indication for use?

15 How may clinical benefit be estimated from  
16 these end points? What additional issues should be  
17 considered by FDA when evaluating indications for use  
18 for devices other than stainless steel instruments?  
19 How can devices constructed from or including  
20 materials other than stainless steel, devices with  
21 complex shapes, devices with hinged or mated surfaces,  
22 or devices with lumens be addressed? How closely

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1 should the experimental treatment conditions for a  
2 product or process indicating a reduction in TSE  
3 infectivity replicate the actual conditions under  
4 which the proposed product or process would actually  
5 be used? Should such issues as instrument cleaning,  
6 conditions which might fix protein to instruments,  
7 possible interactions between new products or  
8 processes and standard cleaning agents, sterilizer  
9 cycles normally used, et cetera, be considered?

10 Finally, considering the current state of  
11 the science and existing investigative methods for  
12 estimating the potential for TSE transmission, can an  
13 indication for the use of complete elimination of TSE  
14 infectivity be validated? These are lengthy and  
15 complex questions. We very much appreciate your  
16 willingness to help us address them today and our next  
17 speaker will be Dr. Elaine Mayhall.

18 DR. MAYHALL: Good morning. My name is  
19 Elaine Mayhall. I'm a reviewer in the Infection  
20 Control Devices Branch. I'm going to give you an  
21 overview of transmissible spongiform encephalopathies  
22 and their transmission. Most of this information

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1 you've seen already but my intent is to get everyone  
2 on the same page leading into the presentations on the  
3 animal model, the statistical considerations and the  
4 risk analysis. Next.

5 Transmissible spongiform encephalopathies  
6 or TSEs are rare progressive neuro-degenerative  
7 diseases which effect both humans and animals. TSEs  
8 result from the accumulation of the abnormal isoform  
9 of a normal host cell protein which causes progressive  
10 neuronal dysfunction. The human TSEs include  
11 idiopathic forms, sporadic Creutzfeldt-Jakob disease  
12 or CJD, which is the most common, and sporadic fatal  
13 familiar insomnia. There are two forms that are  
14 transmissible by ingestion of contaminated tissue,  
15 variant CJD and Kuru and the inherited forms include  
16 familial CJD, familial fatal insomnia, and Gerstmann-  
17 Straussler-Scheinker Syndrome.

18 The animal TSEs include scrapie in sheep,  
19 bovine spongiform encephalopathy or BSE in cattle,  
20 transmissible mink encephalopathy, feline spongiform  
21 and exotic ungulate encephalopathies in zoo animals  
22 and chronic wasting disease in deer and elk. The

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1 pathogenesis of human TSEs originates in a normal  
2 prion protein. A prion is a proteinaceous infectious  
3 particle. The normal isoform of the prion protein is  
4 designated PrPc or PrPsen because it's sensitive to  
5 proteinase K digestion. The protein is encoded by the  
6 PRNP gene and is expressed on the surface of neurons,  
7 glial cells and other cells and its function has not  
8 been determined. Next.

9 The abnormal isoform is designated PrPsc  
10 or PrPres because it's resistant at least partially to  
11 proteinase K digestion. And this abnormal isoform  
12 induces the conversion of the normal isoform through  
13 conformational changes to the abnormal isoform and the  
14 it's the subsequent accumulation of this abnormal  
15 isoform which causes the fatal neurodegenerative  
16 disease. Next.

17 The normal isoform is a monomer and it's  
18 sensitive to proteinase K. It's been found at the  
19 cell surface and is rapidly synthesized and degraded.  
20 The abnormal isoform forms oligamers and polymers and  
21 is resistant at least partially to proteinase K  
22 digestion. The abnormal isoform is found inside

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1 vesicles inside the cell and is slowly synthesized and  
2 degraded. So the presence of the abnormal isoform  
3 induces the conversion of the normal isoform to the  
4 abnormal isoform. The abnormal isoform can be  
5 acquired through a number of sources. One is through  
6 sporadic occurrences, such as a somatic mutation in  
7 the gene, ingestion of the abnormal isoform,  
8 iatrogenic transmission of the abnormal isoform  
9 through surgical instruments and autosomal dominant  
10 inheritance of the abnormal isoform and at least 30  
11 mutations have been described.

12 So for transmission of TSE to occur, you  
13 need -- the abnormal isoform has to be present. For  
14 transmission of the disease requires that the prion be  
15 transferred, usually in a tissue and the tissue would  
16 probably be the central nervous system tissue.  
17 However it can be transferred in other tissues. The  
18 efficiency of transmission is dose related. The risk  
19 of TSE transmission will be determined by one, the  
20 availability of a TSE source, the likely frequency of  
21 a transmissible encounter with a TSE source and an  
22 effective TSE dose. The larger the dose, the more

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1 efficient the transmission.

2 Iatrogenic transmission of Creutzfeldt-  
3 Jakob disease has been reported. The incubation  
4 period ranges from one year to 30 years. And most  
5 cases have been reported for dura mater grafts and  
6 administration of growth hormone. There are seven  
7 cases that have been reported for transmission of TSE  
8 via neuro-surgical instruments. Next slide.

9 All seven of these cases occurred between  
10 1954 and 1980 and all seven occurred in Europe. No  
11 cases were reported in the United States. So how do  
12 we prevent iatrogenic transmission? We know that  
13 human forms of TSE can be transmitted and that  
14 transmission by materials and instruments contaminated  
15 by CNS tissue from CJD patients has occurred. So if  
16 we limit the use of contaminated materials and don't  
17 reuse contaminated instruments, we should be able to  
18 prevent transmission. However, CJD patients are not  
19 always promptly diagnosed in the early stages of  
20 disease.

21 Current recommendations for clinical  
22 practice for reducing TSE transmission indicate that

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1 precautions should be taken with instruments that have  
2 been used for invasive CNS procedures in patients with  
3 dementia of uncertain origin and patients known or  
4 suspected of having TSE.

5 In addition, these precautions are  
6 extended to instruments used for extraneural  
7 procedures on these same types of patients, even  
8 though the risk of transmission is lower. These  
9 recommendations include discarding the instruments,  
10 quarantining the instruments until a diagnosis is  
11 confirmed, or treating the instruments with processes  
12 recommended by CDC which have been shown to have some  
13 in vivo effect in reducing TSE transmission. These  
14 treatments are based on studies that were conducted at  
15 the National Institutes of Health in 1990. Next.

16 Normal sterilization cycles are inadequate  
17 for reducing TSEs. It takes much more rigorous  
18 conditions to reduce TSE. The cycles recommended  
19 include prevacuum steam sterilization at 134 degrees  
20 Celsius for 18 minutes, gravity steam sterilization at  
21 121 degrees for one hour and emersion in one normal  
22 sodium hydroxide for one hour. Next.

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1           These TSE cycles have also been combined  
2 with emersion of the instruments in sodium hydroxide  
3 and some authorities have recommended immersing the  
4 instruments in sodium hypochlorite but all of these  
5 methods are highly corrosive to the instruments and  
6 the sterilizer cycles are unsuitable for heat  
7 sensitive materials. These procedures have not been  
8 systematically studied for clinical efficacy due to  
9 the rarity of CJD and for ethical reasons.

10           With these precautions and treatments in  
11 place, iatrogenic transmission of CJD by CJD  
12 contaminated surgical instruments has not been  
13 reported since 1980. Small epidemiologic studies of  
14 risk factors for CJD have not consistently shown any  
15 statistically significant association between surgery  
16 and CJD. There have been reports of patients that  
17 have been exposed to instruments that have been used  
18 for invasive CNS procedures on patients with  
19 unrecognized CJD. However, to date, none of these  
20 cases have resulted in iatrogenic CJD.

21           The primary TSE source in the United  
22 States is sporadic CJD. It's the most common TSE and

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1 accounts for more than 85 percent of the cases. The  
2 average annual US death rate from CJD is .95 per  
3 million persons. Variant CJD has been described only  
4 once in the United States and that was in a recent  
5 immigrant from the United Kingdom. So does variant  
6 CJD increase the risk of iatrogenic TSE transmission?

7 We know that patients with variant CJD have greater  
8 extra-neural tissue burdens of the abnormal isoform  
9 and they may have atypical and prolonged symptoms  
10 before diagnosis, so the number of patients with pre-  
11 symptomatic variant CJD may be increasing.

12 Hence, there's a concern that the risk of  
13 variant CJD transmission by surgical instruments may  
14 be increasing in areas effected by the TSE epidemic  
15 and may involve other tissues besides CNS tissues.  
16 However, as I pointed out, no -- there have been no  
17 reports of variant CJD originating in the United  
18 States.

19 In summary, TSEs are rare, fatal,  
20 neurodegenerative diseases of humans and animals. TSE  
21 has very rarely been transmitted by contaminated  
22 surgical instruments. Current clinical practice based

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1 on the CDC recommendations may reduce the risk of TSE  
2 transmission by contaminated instruments but is it  
3 possible to further reduce the risk? Any questions?

4 CHAIRMAN EDMISTON: I think what we'll do  
5 is because of the intimacy of your presentations,  
6 we'll wait till the end and bring you all up  
7 separately. Thank you. The next presenter will be  
8 Estelle Russek-Cohen -- excuse me, Cohen. Oh, Dr.  
9 Murphy is going back in cycle?

10 DR. MURPHY: Yes, I'm back.

11 CHAIRMAN EDMISTON: All right.

12 DR. MURPHY: Thank you. We're now going  
13 to discuss some of the experimental design issues that  
14 would be -- that would be involved in considering a  
15 possible product that might claim to reduce the  
16 transmission of TSE. There are potentially three  
17 models that could be presented to us to investigate  
18 this hypothesis. Most of the work that has been done  
19 in the field of TSE has been done with in vivo models.  
20 This is how transmission was first recognized. It's  
21 how most of what we've learned about these diseases  
22 has been learned.

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1           The animal models are quite suitable for  
2 examining transmissibility and we can with these  
3 models, examine not only transmissibility but proxies  
4 for actual surgical instruments. Other assays which  
5 are useful in studying TSEs in general, include  
6 immunoassays to detect the presence of both the normal  
7 and the abnormal prion protein. These were developed  
8 for diagnostic purposes and for use in tissues. They  
9 have not been developed for use on hard surfaces.  
10 They are not strictly quantitative. Their sensitivity  
11 does not equal the animal model and at the present  
12 time it's not really feasible to use those to directly  
13 examine transmissibility.

14           Another tool which has recently become  
15 available is using cell culture to look at the  
16 molecular aspects of the behavior of the prion  
17 proteins. This seems to be a very fruitful model for  
18 basic science studies. At the present time, however,  
19 it's not really feasible for using it to examine in  
20 vivo transmissibility. And it's not clear how we  
21 would study -- how we would study instrument proxies  
22 with cell cultures.

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1           In future, these tools might have more  
2 utility but at the present time, we feel that what we  
3 need to learn for considering a claim for reducing TSE  
4 infectivity on instruments is going to have to be  
5 learned through the use of in vivo models of TSE  
6 transmission. In these models we are going to need a  
7 prion source, a susceptible host animal. We're going  
8 to have to introduce the infectious agent into the  
9 central nervous system. In fact, it can be introduced  
10 outside of the central nervous system but CNS  
11 introduction is most efficient. The host is then  
12 observed for symptoms of TSE disease or after a long  
13 asymptomatic lifespan, is electively sacrificed at a  
14 pre-determined end point close to the end of its  
15 natural lifespan.

16           And finally, the outcome in terms of  
17 establishing infection or not needs to be determined  
18 by directly examining central nervous system for  
19 evidence of TSE infection. There are a number of  
20 potential prion sources which could be used in studies  
21 of TSE transmission. Human prions, most commonly the  
22 sporadic disease is available but studies have been

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1 done with variant CJD and the genetic forms of the  
2 disease which are transmissible. Any of the animal  
3 prions could, of course, be studied. Most of what's  
4 been published has been done with scrapie and more  
5 recently with bovine spongiform encephalopathy. Next.

6 The most common hosts that we see in the  
7 literature nowadays in in vivo studies of TSE  
8 transmission are small mammals; mice, hamsters and  
9 guinea pigs. Other animals have been used over the  
10 years and are susceptible but these animals are easy  
11 and relatively economical to house in large numbers  
12 for long periods of time and to manipulate. As we're  
13 study disease, particularly disease from another  
14 animal species or from man, we do have to consider the  
15 fact that the natural lifespan of these small mammals  
16 is very different from that, perhaps of the original  
17 prion source. The effect that that might have on the  
18 natural history of infection or other aspects of  
19 interpreting the results, of course, is a bit open to  
20 interpretation. And these models can be genetically  
21 altered to carry the normal prion protein of other  
22 species to make them more susceptible to cross species

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1 infection. Next.

2           There are barriers to transmitting prions  
3 between species. It is unusual. Scrapie was first  
4 described in the 1700s, and yet, we have never  
5 documented the transmission of scrapie to man. On the  
6 other hand, BSE which may have arisen from scrapie or  
7 as a mutation because there are some molecular  
8 differences, appears to be much more readily  
9 transmitted to other species. We believe that it has  
10 been transmitted not only to man causing variant CJD  
11 but also to felines and to a variety of exotic  
12 ungulates by contaminated feed.

13           So species barriers can be overcome. In  
14 the laboratory this is most efficiently done by using  
15 a large infecting inoculum and then by serially  
16 passaging an inoculum in the new host. And as  
17 previously mentioned, genetic manipulation of the host  
18 may also be used. Next.

19           We can introduce the prion source by using  
20 whole brain tissue. This is a little bit difficult to  
21 quantitate, however, so it's much more common to use  
22 homogenates of brain tissue. These may be diluted,

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1 serially in some studies. The materials may be pooled  
2 from several sources before they're inoculated in an  
3 experimental model and they may have been frozen for  
4 use. There are not large numbers of human -- of human  
5 brains available for such studies. The National  
6 Institutes of Health have the largest pool of donated  
7 material and of course, that has to be frozen in order  
8 to make it available over a long period of time.  
9 Next.

10 The infectious inoculum can be introduced  
11 into the central nervous system by injection with  
12 needle. This is what was first done and it is still a  
13 very common mode of study. In 1999 Sobalis' group  
14 described inoculating stainless steel wires by letting  
15 them sit in brain homogenate for a period of time.  
16 These are small fine wires. They may be left in situ  
17 in the brain or they may be inserted and then removed  
18 over a period of time. Very recently coated  
19 stainless steel spheres have also been used to  
20 introduce TSEs, although this has been extra-neural  
21 rather than into the central nervous system. Next.

22 There are, of course, differences between

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1 the experimental model and real instruments in the  
2 real world. And this is something that FDA will have  
3 to consider if someone decides to bring us a potential  
4 product for evaluation. In the experimental model,  
5 usually new steel needles or wires or spheres are  
6 inoculated for use. In the real world, we're using  
7 instruments over periods of time so their surfaces  
8 become aged and pitted. They may be steel or they may  
9 be various metal alloys and instruments may contain  
10 other materials as well.

11 They may have complex shapes rather than  
12 the relatively simple shapes of a needle or a wire.  
13 And instruments have hard to clean surfaces. Hinges,  
14 mated surfaces and lumens are particularly hard to  
15 clean, as we've learned in our studies of  
16 sterilization and high level disinfection. Next.

17 This is an example borrowed very kindly  
18 from one of our colleagues of fine wires in the lower  
19 portion of the slide attached to plastic pipet tips.  
20 Above them is a penny for scale and above that is a  
21 small insulin syringe as an example of the relative  
22 size of these wires. And they're actually a little

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1 larger than they would be used in the animal itself  
2 but it's easier to manipulate than when they're glued  
3 to a piece of plastic. Next.

4 This is a drill, the sort of instrument  
5 that would be used perhaps, create a burr hole for a  
6 central nervous system biopsy. As you can see, it's a  
7 rather complex instrument. Cleaning it has to be done  
8 carefully before you reprocess it. Next.

9 These are brain scoops and you can see  
10 there are little almost spoons at the end. They're  
11 very simple instruments to clean, although you do have  
12 to be careful to get the tip exactly clean. Next.

13 This is a bone rongeur. You squeeze the  
14 handle and the little scrape at the tip moves back and  
15 forth scraping up pieces of bone. You can see that  
16 that instrument is going to be very complex to  
17 adequately clean before you can effectively sterilize  
18 it. Next.

19 This is a simple pair of scissors but the  
20 hinged area has picked up quite a lot of blood which  
21 will, again, have to be completely removed before you  
22 can effectively sterilize that instrument. Next.

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1           We have to be aware of the fact that the  
2           prion sources can change over time. A serial  
3           laboratory of passage of prions has in fact, resulted  
4           in the formation of distinct strains of prions with  
5           slightly different characteristics when they're  
6           administered to host animals. Back in 1978 Dickson  
7           and Taylor described two different strains of scrapie  
8           used in the laboratory. One took twice as long as the  
9           other to be inactivated by heat at 126 degrees  
10          centigrade. Obviously, if you were doing a study that  
11          involved heat in activation, which of these two  
12          strains you chose would effect the outcome that you  
13          would obtain. Next.

14                 There are a number of sources of  
15          variability, particularly in animal studies which have  
16          to be considered in investigational study design. Are  
17          you going to use a single brain as the source for your  
18          material in the study or are you going to pool several  
19          different brains? Are you going to prepare your  
20          inoculum on a single occasion or are you going to  
21          prepare it several times, particularly when preparing  
22          a large number of animals? Will all the host animals

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1 be inoculated on a single day or will you do it again  
2 over a period of time? What about the variation in  
3 the actual fact of inoculum? How much material is  
4 going to be left on the inside of the needle when  
5 something is injected? How accurately can you measure  
6 what is on a wire? Next.

7 In terms of maintaining the animals,  
8 again, have they all been inoculated on the same day?  
9 Are we doing the treatment groups together or are we  
10 separating them? Is each treatment group going to be  
11 in its own cage? The small mammals used in these  
12 studies are usually housed four to five per cage. Are  
13 the cages all going to be geographically together on  
14 the same shelf or the same rack in the animal housing  
15 area where they're going to be staying together for a  
16 very long period of time?

17 When doing a study that's going to extend  
18 over the lifespan of a small animal, we have to expect  
19 that inter-current deaths unrelated to TSE may occur.

20 And these have to be accounted for in the statistical  
21 analysis of the results. So in choosing the size of  
22 the population that will be studied, we have to be

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1 prepared to account for this. Next.

2 What about directly examining the central  
3 nervous system, is that necessary or can we just look  
4 for symptoms of typical disease? Well, a study  
5 published this year from Jackson's group showed that  
6 in a number of their investigational groups and I'm  
7 sure the people in the back can't read this slide, the  
8 number of asymptomatic animals who were sacrificed at  
9 a pre-determined time, but turned out to have on  
10 direct investigation of their brains evidence of  
11 asymptomatic TSE infection varied from 20 percent to  
12 80 percent depending on the investigational group.  
13 Obviously, if these animals -- if this study had used  
14 only symptomatic disease as its end point, the results  
15 would have differed. Next slide.

16 We have to decide therefore, whether or  
17 not TSE is present at the time that the animal is  
18 finally examined, whether it's sacrificed  
19 symptomatically or sacrificed because of disease.  
20 After all, it is the presence or absence of TSE rather  
21 than just symptoms which is the end point of these  
22 studies. Next.

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1           We need to look at how closely does the  
2 experimental process reflect actual clinical practice.

3           Surgical instruments, obviously, are in use, after  
4 use they're cleaned, they're packaged for  
5 sterilization and then they're re-sterilized after  
6 each use. Will the investigational model that is used  
7 to propose a product to FDA incorporate all of these  
8 steps? Next.

9           Will cleaning of an instrument differ from  
10 the cleaning of a 5 millimeter wire? How is the  
11 technique, the cleaning agents, et cetera, that will  
12 be used going to be dealt with? Will cleaning a small  
13 wire remove so much inoculum which has already been  
14 dried onto the wire, that the outcome of the  
15 experiment, in fact, could be effected? Will we  
16 remove too much of the inoculum if the instrument  
17 surrogate is, in fact, washed? And how are we going  
18 to be able to measure that? We're dealing with very,  
19 very small amounts of material. Next.

20           This is an example of an ultrasonic  
21 machine cleaner as used in hospitals. As you can see,  
22 it's a -- well, it's more than a glorified dishwasher.

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1 It really does hold the instruments in an open shape.  
2 It exposes to them to water of varying temperatures,  
3 to detergents and to enzymatic cleaners and even after  
4 the instruments have gone through such a machine, they  
5 do need to be directly inspected to make sure that, in  
6 fact, they have been thoroughly cleaned. Next.

7 Again, the five millimeter wires versus  
8 that is a little bit difficult and how are we going to  
9 package them for sterilization, the same way as we  
10 would an instrument? Next.

11 This is an example of the small wires that  
12 you saw on an earlier slide, glued to the plastic  
13 pipet tips being suspended in a container so that they  
14 may either have material dried on them for a period of  
15 time. They may be subjected to a treatment in this  
16 fashion. They could, of course, be put into a  
17 sterilizer in this fashion. How we would deal with  
18 these in an ultrasonic machine cleaner, however, we  
19 can speculate. I think that investigators are very  
20 ingenious people and they could come up with  
21 something. Certainly, if you have a battery of wires  
22 attached to a lid in this manner, you could simulate a

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1 cleaning process with them. Next.

2 This is an instrument in a plastic pouch.

3 This is one way that things are packaged for  
4 instrumentation, a single instrument or just a few  
5 instruments in a pack but we may also put them into  
6 large packs which we wrap or next slide, into rigid  
7 containers of various sizes. These are obviously  
8 intended to hold large numbers of instruments for  
9 sterilization. Next.

10 Will cleaning, if it is part of the  
11 investigational design, use the standard products that  
12 are used in clinical practice right now? Will it use  
13 the sterilizer cycles which are normally used in  
14 hospitals rather than a sterilizer cycle used --  
15 designed particularly for the experiment? Next.

16 What end points do we need to consider in  
17 these in vivo models of TSE transmission? The end  
18 points reported in the literature include median  
19 incubation period to symptoms, median survival,  
20 percent survival and log reduction in infectivity.  
21 Next.

22 These end points are calculated rather

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1 than directly measured. A control curve is created by  
2 administering serial dilutions of the untreated  
3 inoculate which, of course, will be treated in the  
4 investigational animals. The control animals will  
5 receive serial dilutions of untreated material.  
6 Obviously the more dilute it becomes, it eventually  
7 will reach the point, we hope where animals do not  
8 become infected. And then the outcomes in the  
9 experimental group are compared to the outcomes in the  
10 various control groups. Next.

11 The median incubation period to symptoms  
12 increases as investigational animals receive  
13 progressively smaller doses of infectious material.  
14 This has been demonstrated on numerous occasions in  
15 the published literature. The survival without  
16 infection begins to occur below the infectious 100  
17 dose. The infectious 100 dose is the minimal dose  
18 that will effect 100 percent of the animal population.

19 When you get down to the infectious 50 dose, you  
20 expect that half of the exposed animals will survive  
21 without infection, include without infection of the  
22 direct brain investigation. Now, log reduction in

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1 infectivity as an end point is the end point most  
2 frequently described in the literature. Therefore, we  
3 are going to spend a little time on it. One of the  
4 things that you have to remember in interpreting this  
5 end point is that the magnitude of the central nervous  
6 system infection that can be established in a host  
7 model will vary depending on the prion source and the  
8 animal that you choose for your experiments and in the  
9 published literature the degree of infectivity, the  
10 lethal 50 dose per gram of brain tissue, has tended to  
11 vary between  $10^7$  and  $10^{11}$  depending as I said on the  
12 type of prion and the type of animal that you choose  
13 to use.

14 Now, if you're looking at a study that's  
15 going to reduce infectivity by a given number of logs,  
16 the number of logs that you start with plus the number  
17 of logs by which you further reduce infectivity will,  
18 of course, determine your end point. If you start  
19 with a model that gives you  $10^{11}$  infectious doses per  
20 gram of brain tissue, you can go down quite ways and  
21 perhaps still have a considerable amount of  
22 infectivity left. If you use a model that establishes

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1 a lower level of infectivity, you may reduce the  
2 infectivity by roughly the same amount as the other  
3 model. You may reach an end point where it's going to  
4 be very difficult to measure whether you've got  $10^2$  or  
5  $10^1$  infectious doses left and remember you're making  
6 these measurements by comparing them to the control  
7 curve. Next.

8 The log reduction is the reduction from  
9 the exact inoculum that was placed into the central  
10 nervous system to what we estimate is left in the  
11 surviving hosts. We have some problem exactly  
12 measuring some times what has been put into the host  
13 model, either injected with a needle or adhering to a  
14 wire. And that reduction, however, is what we're  
15 going to have to be looking at. The lower limit of  
16 detection for these in vivo studies has not been  
17 determined. Next.

18 We have to look for a measurable  
19 difference between the experimental and control  
20 groups. Is it there? What is the magnitude of that  
21 difference? How certain are we of the reality of that  
22 difference between the investigational and control

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1 groups? Next.

2 Is that experimental difference  
3 statistically significant? Is it clinically  
4 significant, a rather difficult to define end point.  
5 Next.

6 Remember that different model systems will  
7 produce different results and different prion  
8 characteristics such as sensitivity to heat and  
9 activation might also effect the results that might be  
10 seen in a particular experimental design. The  
11 magnitude of the infection in a given experimental  
12 design will also effect the results. Next.

13 Are the in vivo experimental models of TSE  
14 transmission results clinically relevant? Should  
15 current clinical practice be altered on the basis of  
16 such experimental results? On the basis of the  
17 studies published by the National Institutes of Health  
18 in the early and mid-1980s which showed that certain  
19 types of sterilization processes had no effects on  
20 prions and that other types of sterilization processes  
21 did in fact, reduce TSE infectivity, clinical practice  
22 was changed and various groups such as the Centers for

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1 Disease Control and other authorities did make  
2 recommendations which have changed clinical practice.

3 So in fact, we have changed clinical practice on the  
4 basis of animal studies. Next.

5 When considering a product or process  
6 which might reduce TSE transmission, we have to  
7 consider the risk/benefit ratio. Next.

8 The benefit that might be derived from a  
9 product or process which could reduce TSE transmission  
10 would be a reduction in the risk of transmitting  
11 Jakob-Creutzfeldt disease and other TSEs by  
12 contaminated surgical instruments. Any risks, yes. A  
13 false sense of security about the risk of transmitting  
14 TSE now by contaminated surgical instruments, perhaps  
15 on the part of health care workers, a failure to  
16 adequately follow the practices currently recommended  
17 to reduce that risk of TSE transmission by  
18 contaminated instruments. Perhaps health care workers  
19 might pay less attention to identifying patients with  
20 possible CJD before invasive procedures, especially  
21 neurosurgical procedures. Perhaps we might pay less  
22 attention to quarantining, discarding or specially

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1 processing instruments used in invasive procedures on  
2 patients with possible or definite CJD. Might we pay  
3 less attention to carefully cleaning contaminated  
4 surgical instruments if we thought we had a backup  
5 product to reduce the risk. Might there be less  
6 willingness to follow the current CDC recommendations  
7 for handling possibly contaminated instruments, less  
8 willingness to discard hard to clean contaminated  
9 instruments, possibly contaminated by CJD.

10 Is the clinical benefit of approving  
11 potential products or processes which reduce TSE  
12 transmission from its current level significant? Does  
13 this benefit outweigh the possible risks? Next.

14 These are the questions with which we hope  
15 that you, panel members, will be able to assist us.  
16 Thank you.

17 CHAIRMAN EDMISTON: Thank you, Dr. Murphy.  
18 On further reflection, I think what we're going to do  
19 here because of some new members on this panel, is  
20 that we'll break this in two sections. Before we go  
21 on to statistics and risk, I think the panel members  
22 should be given the opportunity to address both your

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1 presentations and Dr. Mayhall's. Are there any panel  
2 members who would like to ask a question at this time?

3 Yes.

4 DR. LURIE: Thank you. First, I want to  
5 thank the FDA for sending out this material  
6 beforehand, because if this was the first time I'd  
7 seen it, I would have been more confused than I am  
8 now. I guess I have two questions that are related  
9 and either one of you would be -- or anybody else who  
10 could answer would be great. I'm wondering is there  
11 is such thing as asymptomatic human disease. Does  
12 this entity exist or do all people who are infected  
13 with the varying Jakob-Creutzfeldt develop symptoms  
14 and also looking at the numbers that we were given of  
15 .95 people per million who get this disease, I suppose  
16 that's in the United States, over the last 25 years  
17 since 1980, I calculated that to be about 3,000 people  
18 who would have been infected with this, am I to  
19 understand then that with the 3,000 people that we  
20 assume have ben infected with this, that there have no  
21 been transmission -- there has been no transmission of  
22 this disease?

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1 DR. MURPHY: There have been no reported  
2 transmissions of Jakob-Creutzfeldt disease or any of  
3 the other TSEs which infect humans by contaminated  
4 surgical instruments reported since 1980. That's  
5 reported cases. Has transmission occurred without  
6 being recognized? We don't know. Statistically,  
7 there is a possibility that patients have undergone  
8 surgical procedures, that instruments have been  
9 contaminated, have not been processed -- have not been  
10 discarded, and have not been processed in a manner  
11 which might reliably significantly reduce TSE  
12 transmission. That is, of course, a possibility.

13 And actually one of our later speakers  
14 will give you the approximate estimates of how often  
15 that might occur in the United States based on what we  
16 know now about the current levels of prevalence of  
17 Jakob-Creutzfeldt disease in the population and our  
18 estimates in terms of numbers of neurosurgical  
19 procedures, instruments used, et cetera. We'll be  
20 using a model that was first developed by our  
21 colleagues in the United Kingdom and we've simply  
22 plugged the US numbers into that.

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1           The natural history of the TSEs, this is  
2 based primarily on animal models, but there is human  
3 data to back this up as well, is that there is an  
4 extremely long incubation period before symptoms  
5 occur. And during that incubation period, the  
6 abnormal prions are beginning to accumulate in various  
7 tissues, primarily in the central nervous system but  
8 in other tissues as well. In animal studies of TSE,  
9 you can take animals who have been exposed to TSE, who  
10 have not yet developed symptoms and inoculate not only  
11 their central nervous system tissues but extraneural  
12 tissues as well into recipient host and successfully  
13 transmit disease.

14           In man this has probably also occurred and  
15 may well be the source of infection of dura mater and  
16 of human growth hormone and gonadotropins where  
17 material from humans dying either of dementia or of  
18 some intercurrent event and who are not recognized, of  
19 course, to have CJD had their tissues donated. Those  
20 tissues were processed with processes that did not  
21 inactivate prions and the material was then given to  
22 other hosts who then went on to develop Jakob-

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1 Creutzfeldt disease.

2           There is one of the two cases of variant  
3 Jakob-Creutzfeldt disease which has been transmitted  
4 by blood transfusion occurred in an elderly gentleman  
5 who received a transfusion from a patient who later on  
6 developed symptoms and died of variant CJD but was  
7 asymptomatic at the time of donating blood. That  
8 donor, of course, apparently transmitted the disease  
9 because the recipient host, when he died of an event  
10 that was totally unrelated to TSE had consented to  
11 autopsy. His brain was examined. He did have  
12 evidence of TSE infection although he had not  
13 developed symptoms. So yes, there is an infectious  
14 pre-symptomatic period which extends, we believe, over  
15 a period of years and we have no way of reliably  
16 determining the presence of that until the patient, in  
17 fact, develops symptoms unless we're following the  
18 patient, we know that they've been exposed and we have  
19 a very sensitive assay. And even then, predicting our  
20 ability to find the TSE outside of the central nervous  
21 system is very difficult. The sensitivity of the  
22 assays is not great.

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1                   This is something that our colleagues in  
2 the United Kingdom, of course, are concerned about  
3 because variant CJD has higher extraneural prion  
4 levels, particularly in lymphoid tissues such as  
5 tonsils.

6                   CHAIRMAN EDMISTON: Dr. Priola.

7                   DR. PRIOLA: One quick question. Even  
8 though there's been no instance in the US of  
9 iatrogenically transmitted sporadic CJD, there have  
10 been instances of surgical instruments being used on a  
11 patient was later diagnosed with CJD, those  
12 instruments being used on other people. Have those  
13 cases, individuals been followed? Maybe this is more a  
14 question for this CDC. Are those individuals being  
15 followed to see if they eventually develop sporadic --  
16 or iatrogenic CJD because that would give you some  
17 indication of potential incubation times following  
18 exposure.

19                   DR. MURPHY: We believe that at least some  
20 of them are being followed, but we do not know how  
21 carefully all of them are being followed. All that we  
22 know for sure at the present time is that no

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1 symptomatic transmission of disease has been reported  
2 from those exposures.

3 CHAIRMAN EDMISTON: Yes.

4 DR. SCHONBERGER: Yeah, on one of the  
5 tables, I guess it's on page 4, I may help because I  
6 had occasion last year to try to update some of those  
7 numbers. It may give people here some idea that this  
8 is an ongoing outbreak, that is for the dura mater and  
9 for the graft hormone cases particularly where the  
10 number at least through mid-2004 where we have 114, it  
11 was, at that point 169 --

12 DR. TELLING: Larry, excuse me, which  
13 document are you referring to here?

14 DR. SCHONBERGER: I'm sorry, this is the -  
15 - I guess it was --

16 DR. TELLING: Oh, the slide presentation.

17 DR. SCHONBERGER: Yes, Sheila's first  
18 slide presentation, Sheila Murphy's.

19 DR. MURPHY: It would have been Dr.  
20 Mayhall's presentation. It's the table that was  
21 derived from that --

22 DR. SCHONBERGER: Oh, yes, this was

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1 Mayhall.

2 DR. MURPHY: -- report from the National  
3 Institutes of Health, their figures as of 2000. You  
4 do have that exact reference in your panel packets.

5 DR. SCHONBERGER: Right.

6 DR. MURPHY: This is it, yes.

7 DR. SCHONBERGER: I just wanted to -- so  
8 the dura mater graft as of mid-2004 was 169 and the  
9 growth hormone was 179. Now part of the reason for  
10 the big increase in the dura mater is Japan which  
11 ended up now with 112 cases themselves. So Japan is  
12 having a major outbreak of the dura mater associated  
13 disease. The other thing to correct and it's  
14 something that probably shouldn't continue to be  
15 disseminated is that the neurosurgery from that  
16 article, Paul made a mistake in terms of the four in  
17 England, it should have been three and then there was  
18 one from --

19 DR. MURPHY: One from France.

20 DR. SCHONBERGER: So the total is really  
21 not seven but six. And that's just -- I don't know if  
22 it was a typographical or something that he did. So

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1 we probably shouldn't continue to disseminate that but  
2 as far as I know, the total there is six.

3 DR. MURPHY: Yeah, we were only able to  
4 find the four published patients.

5 DR. SCHONBERGER: Right, no, that's --

6 DR. MURPHY: That was a point in most  
7 other publications.

8 DR. SCHONBERGER: In looking it up I  
9 talked to Bob Will who would know what happened in the  
10 UK and I asked him about it and he said, no, there was  
11 confusion about that number. So it should be -- he  
12 had three, I guess and there was one from France, was  
13 it?

14 DR. MURPHY: There was one from France,  
15 three from the United Kingdom and the two electrodes  
16 are from Switzerland.

17 CHAIRMAN EDMISTON: Any further questions?  
18 Yes.

19 MS. SANHIRAJ: You've been talking about  
20 the quarantine of instruments and I --

21 DR. MURPHY: I'm sorry, I can't hear you.

22 CHAIRMAN EDMISTON: Speak into the

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1 microphone.

2 MS. SANHIRAJ: About the quarantine the  
3 instruments, the surgical instruments. I just want to  
4 know is that any procedure, any special procedure to  
5 do that or just soaking in enzyme or what?

6 DR. MURPHY: I'm sorry, are you referring  
7 to routine processing of the --

8 MS. SANHIRAJ: No quarantining the  
9 instruments.

10 CHAIRMAN EDMISTON: You mean after  
11 surgery.

12 MS. SANHIRAJ: After surgery.

13 CHAIRMAN EDMISTON: After a patient has  
14 been identified or a suspected patient.

15 MS. SANHIRAJ: Correct.

16 CHAIRMAN EDMISTON: What you're asking is  
17 there a standard practice for quarantining  
18 instruments.

19 MS. SANHIRAJ: Correct.

20 DR. MURPHY: Yes, if you are going to be  
21 performing an invasive procedure on a patient whom you  
22 suspect that CJD may be the diagnosis, the routine

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1 that is recommended for all hospitals would be that  
2 you either use disposal instruments and dispose of  
3 them completely and inevitably after the procedure or  
4 you quarantine the instruments and do nothing with  
5 them other than to keep them moist and physically  
6 clean them but you do not physically reprocess them.  
7 You certainly do not put them back into use until you  
8 know what the diagnosis on the patient turns out to  
9 be.

10 If the patient ends up being shown to  
11 definitely have a diagnosis which is not CJD, then you  
12 may internally reprocess those instruments and put  
13 them back into use. If the patient turns out to have  
14 CJD, then you're going to have to discard those  
15 instruments or process them as you would for a CJD  
16 infected patient.

17 CHAIRMAN EDMISTON: Let me move to the  
18 left for a moment. Dr. Grammer or Jarvis, do you have  
19 questions? Dr. Grammer?

20 DR. GRAMMER: Yes, I'm an immunologist and  
21 so immunoassays are one of my favorite things to talk  
22 about. In your handout, where it says, you know,

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1 about the transmissibility in the instrument and so on  
2 and so forth, just to, you know, step back from that,  
3 and say that to, you know, get at the quarantining  
4 thing is -- I can't imagine that it -- an immunoassay  
5 can't be developed to check, you know, the instruments  
6 when they first come out of surgery with all that gunk  
7 on them and, you know, extract them and look for  
8 abnormal prion protein. I mean, that would seem to me  
9 to be much easier than trying to sterilize every  
10 instrument in the United States ever used on a patient  
11 with some, I don't know, caustic, you know,  
12 unbelievable stuff and also gets totally away from all  
13 this animal models and how long -- I mean, that sounds  
14 very expensive. Immunoassays are pretty cheap to  
15 develop.

16 CHAIRMAN EDMISTON: Let me just jump in  
17 for a minute and just make a few comments. The way it  
18 functions today in hospitals, we look at a couple of  
19 different issues. And those of us who deal with this  
20 matter day in and day out, we look at two issues; one,  
21 the standard methods for disinfection and  
22 sterilization of our instruments and we also look at

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1 the relative risk of our patient population.

2           So I think with those two things, those  
3 are the issues that we've addressed. I think the  
4 purpose of this meeting for the purpose of the FDA, is  
5 to sort of fine tune what their requirements are going  
6 to be if they have to evaluate new devices or products  
7 that come forward. And I think that's really the  
8 issue that we're going to be addressing here. There's  
9 some pragmatic issues and there are some hypothetical  
10 considerations, but I think right now we're dealing  
11 with a more pragmatic perspective, what's currently  
12 available, especially within the hospital environment  
13 because most of us don't have the types of resources  
14 to do those kinds of analysis that would be on a much  
15 more basic level.

16           DR. GRAMMER: Well, I would just say that,  
17 you know, like pregnancy tests that are very, very --  
18 I mean, it's a dipstick thing, if you really, you  
19 know, find somebody who can develop a really good  
20 antibody to distinguish the one from the other, it's  
21 not rocket science.

22           DR. MURPHY: Well, the problem is that at

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1 the present time, studies have not been done to take  
2 those tissue based assays and apply them to material  
3 washed off instruments and then look at that in an  
4 animal model to determine what the sensitivity of the  
5 assay with respect to transmission or risk of  
6 transmission really would be. It's actually not that  
7 easy to get material off instruments and be sure that  
8 you've gotten every single bit off. That's one of the  
9 problems in instrument cleaning in reality.

10 CHAIRMAN EDMISTON: Dr. Jarvis.

11 DR. JARVIS: A couple of questions and  
12 maybe Larry, you know, this better than others, of  
13 those six or seven or whatever the number of  
14 instrument, electrodes and neurosurgical instruments  
15 that have been associated with transmission, how many  
16 of those have had well-documented reporting of what  
17 type of sterilization was done on them to know whether  
18 they actually met even the minimum US standards for  
19 routine instruments?

20 DR. MURPHY: The amount of information is  
21 limited. We do know that the electrodes were  
22 processed by a formaldehyde vapor process. They were

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1 cleaned, they were treated with the formaldehyde vapor  
2 sterilization process for 48 hours and then they were  
3 reused. Actually one of those two electrodes was  
4 collected and later sent to the NIH. And about two  
5 years after it has transmitted disease to a patient,  
6 transmitted disease to a chimpanzee. So the process  
7 used for the electrodes were things that were later  
8 shown in the 1980s to be absolutely ineffective in TSE  
9 inactivation. We have very limited information on the  
10 other four cases that involve surgical instruments.

11 We believe that one of the hospitals used  
12 dry heat for instrument reprocessing and for the three  
13 in England, it's not mentioned in the studies.

14 DR. JARVIS: Has there ever been a case  
15 reported in the United States where even the minimal  
16 not the CJD recommendation but even the minimal  
17 surgical instrument sterilization parameters have been  
18 used where transmission has occurred?

19 DR. MURPHY: There are no instances  
20 reported in the United States of CJD transmitted by  
21 contaminated instruments, no matter how the  
22 instruments were processed and nothing has been

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1 reported in literature since 1980. The --

2 CHAIRMAN EDMISTON: I'm sorry, go ahead.

3 DR. MURPHY: I was just going to say the  
4 first three cases of instrument transmission occurred  
5 in the 1950s before the transmissibility of Jakob-  
6 Creutzfeldt disease was recognized.

7 CHAIRMAN EDMISTON: Ms. Howe?

8 MS. HOWE: Thank you. I have a question  
9 for Dr. Mayhall. You made a reference to recommended  
10 procedures for treating the contaminated instruments  
11 that for some reason that study wasn't being followed  
12 for ethical reasons. It didn't appear on your slide  
13 but could you elaborate on your side note about the  
14 ethical concerns?

15 DR. MURPHY: I can probably better comment  
16 on that. The comment was that they have not been  
17 systematically studied. Any hospital -- a large  
18 referral hospital that sees lots of patients for  
19 neurosurgery may see one or perhaps two patients a  
20 year that have Jakob-Creutzfeldt disease. I'm basing  
21 that on my own personal experience at an academic  
22 medical center for many, many years. When you have a

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1 patient, you don't say, "Well, I'm going to do this  
2 for this patient and that for that patient". If there  
3 are recommendations from the CDC, that's what you  
4 follow. So it's not something that we've ever been  
5 able to study systematically in terms of saying,  
6 "We'll treat the instruments from this patient in this  
7 fashion and the instruments from this patient in that  
8 fashion. That's what we meant by that.

9 MS. HOWE: Thank you.

10 CHAIRMAN EDMISTON: One more comment. Mr.  
11 Telling, I think you had a question.

12 DR. TELLING: Well, no, a comment actually  
13 with respect to Dr. Grammer's question. The issue  
14 relates to being able to distinguish the normal prion  
15 protein from the abnormal prion protein with respect  
16 to immunoassay. Now, so treatments would be required  
17 to actually destroy immunoreactivity of the normal  
18 prion protein and only see the disease associated so  
19 that raises issues of sensitivity. Now there are  
20 scrapie specific -- or there have been reports of  
21 scrapie specific monoclonal antibodies that may, in the  
22 future be useful for such approaches but most

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1 importantly these issues basically related to  
2 sensitivity. The sensitive to the current  
3 immunoassays are not anywhere in the same order of  
4 magnitude as the available bioassays, although they  
5 are under development. There is a promising approach  
6 from USCF a confirmation dependent immunoassay which  
7 is claimed to be as sensitive as the currently  
8 available bioassays.

9 DR. GRAMMER: Yeah, I think that there are  
10 a number of technology companies out there now with  
11 bioterrorism looking at how to detect minuscule  
12 amounts of let's say staph enterotoxin B and so on.  
13 So the sensitivity of those assays is going down to  
14 the fentogram level. I mean, it totally is.

15 CHAIRMAN EDMISTON: I think we should move  
16 on now. Let me pass around to the panel members some  
17 show and tell here. It's a hemostat and there's also  
18 a five and 10 millimeter stainless steel wire and I  
19 think one of the issues that we're going to need to  
20 address is the relevancy of these models. And I'd  
21 like you to look at this very, very carefully because  
22 there's a big difference between looking at a

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1 stainless steel wire as opposed to a surgical  
2 instrument. And without further ado, let's move onto  
3 our next speaker which would be Estelle Russek-Cohen.  
4 Dr. Cohen.

5 DR. COHEN: Good morning. Today I'm going  
6 to be talking about statistical considerations, mainly  
7 design and analysis of these animal model studies. I  
8 promise to keep it formula light because I've always  
9 discovered that doesn't always work very well.

10 LT. COLBURN: Excuse me, Dr. Russek. It's  
11 Slide 83.

12 DR. COHEN: I'm waiting for my slides.  
13 That's all right. I'm the team leader of a  
14 Diagnostics Branch, so I would love to see an  
15 immunoassay that comes to FDA but to my knowledge, we  
16 don't have them right now. I'm in the Division of  
17 Biostatistics in the Office of Surveillance and  
18 Biometrics in the Center for Devices and Radiological  
19 Health. Next slide.

20 In my talk, I'm going to introduce some  
21 minimal background information. And I'm going to talk  
22 about some key components, some study designs with

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1 these animal models. I'm going to contrast some of  
2 the study design issues when you look at a log  
3 reduction end point versus improving survival or time  
4 until first symptoms.

5 I'll talk a little bit conceptually about  
6 the data analysis issues and some of the conclusions.

7 At FDA when a company comes, we ask them to provide  
8 valid scientific evidence. The studies presented must  
9 support the intended use claim. The study  
10 requirements, the product must be tested to support  
11 labeling instructions and we ask that the conclusions  
12 must have a degree of confidence for example,  
13 statistical significance.

14 There have been a number of studies that  
15 have investigated different types of disinfectants  
16 using various kinds of animal models, as Dr. Murphy  
17 has mentioned. These studies tend to involve one to  
18 three cages of animals per treatment, four to 12  
19 animals per treatment. They often use a single source  
20 of TSE infected brain material. Perhaps it's a  
21 composite anywhere from one to five grains. They use  
22 infected homogenate or potentially, as Dr. Murphy

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1 indicated, they may use a wire on which the material  
2 has been essentially exposed and they use, perhaps one  
3 or two batches of cleaner or disinfectant and its all  
4 done in very controlled research environment.

5           There are some key components to all the  
6 study designs that are potentially for discussion. On  
7 each animal one can record the time until death or  
8 time until symptoms at which point the median survival  
9 or median time until first symptoms can be recorded  
10 for treatment. It's also possible one can look at a  
11 dichotomy and look at whether an animal survives or  
12 does not survive beyond the fixed time period in which  
13 case percent survival could be recorded. The  
14 advantage of time until death or time until symptoms  
15 is that one can consider competing causes of death in  
16 the analysis. These studies usually require a  
17 lengthy incubation period and often a one to two-year  
18 study is needed. Next.

19           For competing causes of death, ignoring  
20 them invariably introduces bias because there are more  
21 competing causes of death potentially available to  
22 animal survivals. If an animal dies, you would expect

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1 that it would be necropsied to confirm whether or not  
2 that animal in fact, has prion disease. If an animal  
3 has prion disease at the time of death but the death  
4 is not due to prion disease, we can consider it as a  
5 death due to prion disease.

6 There are some limitations which my  
7 colleague has eluded to but I think they're worth  
8 mentioning at this stage because they do have  
9 relevance in terms of data analysis. One needs to ask  
10 how much material is actually sticking to these wires?

11 Does it vary within treatment? Does it depend on the  
12 geometry of the wire or perhaps the material? Does it  
13 depend on the matrix and does homogenizing the  
14 material impact the results, does it impact how much  
15 it sticks to the wire? There's also the fundamental  
16 issue of how does it depend on the animal model and  
17 the type of TSE and of course, there's the relevance  
18 to humans. Next.

19 In experimental design, one of the things  
20 we worry about is potential extraneous variables that  
21 might essentially confound conclusions. We want clean  
22 experimental designs. Slow the technician in doing

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1 surgery may possibly impact the result. There's  
2 animal variation. These animals are often housed four  
3 to five animals in a cage. The cages are in  
4 batteries. There can be variation in the strength in  
5 the initial inoculate. And there's lots of wide  
6 variation in the product. Next.

7 This is an example of a cage battery.  
8 Working with small animals is very different from the  
9 human clinical trial where patients come in one at a  
10 time. This is called a mouse condominium and it has  
11 36 cages. Each one can house four or five animals.  
12 This was just photocopied out of a catalog. Hamsters  
13 are a bit bigger so you might get 25, 30 cages from a  
14 battery. Guinea pigs are even bigger still and you  
15 might get fewer animals in a cage. Well, one of the  
16 reasons it's important to know is that animals within  
17 the same cage are not the same as animals in different  
18 cages. They're in a very close quarters for an entire  
19 year. They impact each other. They share a common  
20 watering system, a common feeding system and there's  
21 invariably some dependence that one tends to observe  
22 when one looks at animals within the same cage. Next.

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1           So there's some basic properties of good  
2 experimental design and I've taught this to students  
3 on a number of occasions. This is a quote from D.R.  
4 Cox' planning of experiments. "Properties of good  
5 experimental design, absence of systematic bias,  
6 precision of the end point, the range of validity,  
7 simplicity of the study and calculation of  
8 uncertainty." Next.

9           In the context of these studies, absence  
10 of systematic error to the extent that we can, we  
11 should do everything we can to reduce bias. The  
12 precision of the end point as a statistician I will  
13 tell you that tied into that is preferable to a yes or  
14 no survival end point. Range of validity, I want to  
15 make sure that extraneous variables are accounted for  
16 and I want to know whether they impact performance.  
17 For example, if I get a different result with  
18 inoculate 1 than I do inoculate 2, that raises some  
19 concern.

20           Simplicity speaks for itself and we'll  
21 see. There's also a calculation of uncertainty. You  
22 ask in this context perhaps the report compensates for

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1 levels of significance. One of the ways we reduce  
2 bias is by a technique that's commonly used both in  
3 human and animal clinical trials and we reduce bias by  
4 a randomization, essentially a coin toss to decide  
5 which animals get to go with which cage.

6 So one of the fundamentals we would ask is  
7 that this randomization of animals to cages and then  
8 we randomize cages to treatments, randomization of  
9 order in which the treatment is administered is also  
10 done to reduce bias. We would ask just as we do in  
11 human clinical trials, that there be a concurrent  
12 application of both experimental and control groups.  
13 As I eluded to when I showed you the picture of the  
14 cage battery, these animals are often housed in cages  
15 in very close proximity to each other for extended  
16 lengths of time. Typically in these studies, each  
17 cage is randomized for a single treatment; thus, each  
18 cage is fundamentally a single experimental unit.

19 Observations within the cage are not  
20 independent pieces of information and this is not just  
21 because the disease is potentially infectious. And we  
22 would expect that the analysis submitted would reflect

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1 this, and I would point out that this is standard for  
2 veterinary submissions at the FDA. Quantifying  
3 benefit; by far the most common end point we see in  
4 this literature is this log reduction end point. So  
5 for example, a six-log reduction end point would  
6 correspond to if I start with one million infectious  
7 particles per gram of brain tissue, then one particle  
8 will remain after I use the product.

9 So, for example, if I start off before the  
10 product is applied with about  $10^8$  I believe it's IB  
11 per gram of tissue, afterwards I would be left with 10  
12 squared per gram of tissue. I will note that, as my  
13 colleague noted, you can have an inoculate that goes  
14 anywhere from  $10^7$  to  $10^{11}$  on six log reduction might  
15 still result in anywhere from  $10^1$  to  $10^5$  particles per  
16 gram of tissue and so there could be a considerable  
17 amount remaining afterwards depending upon the amount  
18 of the inoculate to begin with. It's the kind of an  
19 end point that's very, very common in virology and  
20 bacteriology.

21 For the controls in a log reduction end  
22 point, i.e., individual animals that perhaps have not

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1 had any disinfectant applied, the controls are used to  
2 establish a dilution curve or standard curve. Control  
3 animals will be exposed to varying levels of infected  
4 material. The TSE infected inoculate is diluted at a  
5 series of 10-fold dilutions so that a single 10-fold  
6 dilution means one part TSE infected brain and nine  
7 parts something else. One would want to know how that  
8 dilution is prepared and does it impact the material  
9 actually sticking to the wire.

10 For the treatment using the product, you  
11 would tend to use undiluted homogenate to infect the  
12 wire and then you would apply a product, as my  
13 colleague indicated, to disinfect as you would expect  
14 users to use this device in conjunction with labeling  
15 instructions. As a control you would use wires to  
16 infect clean animals and you would do everything for  
17 the treated group as you would for your controls and  
18 then you would see which dilution level it compares  
19 to. So let me give you some hypothetical data. If I  
20 describe a dilution level as minus the log of the  
21 proportion of the infected material, a dilution level  
22 of one would correspond to 10 percent infected

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1 material or .01 or  $10^{-1}$  so that would be a dilution  
2 level of one.

3 You have to assume that there are enough  
4 animals for each dilution level to reasonably estimate  
5 percent survival or median survival for each of those  
6 end points. Next.

7 This is my graph. This is an example with  
8 -- this is an example. The bars in blue correspond to  
9 percent survival to each of the various dilution  
10 levels. I elected to do percent survival rather than  
11 median survival because median survival will depend  
12 upon which animal model you pick and I think we're  
13 seeking the advice of the panel to say which animal  
14 model, if any, is appropriate. Okay, but the idea is  
15 pretty conceptually the same. Instead of saying  
16 percent survival, you might have median survival along  
17 the Y axis.

18 You can see my red line going across.  
19 Each of the blue bars corresponds to the treatment --  
20 to the controls and then the red bar would be the  
21 treated product. The animals that have been treated  
22 with the product, if you take a look, I think I have

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1 it done in about 98 percent, I'm having trouble  
2 reading from here, that falls somewhere between six  
3 and seven. So one would say you have a log reduction  
4 somewhere between six and seven. This is the indirect  
5 way one would get at the log reduction end point.  
6 Next.

7 So let me point out some of the  
8 limitations of the log reduction study. There's some  
9 complex design issues because you need a certain  
10 number of different types of controls, one for each  
11 dilution level. It's hard to balance a large number  
12 of groups across various extraneous factors and it  
13 also has the potential for using sponsor resources,  
14 lots of control animals. It's an indirect end point.

15 It assumes that the log reduction does not depend on  
16 the size of the initial inoculate and it assumes that  
17 we know how much is sticking to the wire at each  
18 level. Next.

19 One possibility is to go to a much simpler  
20 study design where there's a single disinfectant group  
21 and a single control group. Of course, in this  
22 setting one cannot do a log reduction end point. You

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1 would use standard operating procedures with untreated  
2 homogenate plus wire but you would still measure  
3 either survival or time until death or time until the  
4 onset of symptoms. I will point out that some animal  
5 care in these communities will not be happy about  
6 waiting until time of death because this is pretty  
7 painful towards the end of an animal's lifetime and so  
8 time until first symptoms might be more acceptable.

9 This is a simpler design fundamentally  
10 because there's fewer treatments. It's easier to  
11 control extraneous factors and the analysis and sample  
12 size makes it much easier to determine. Because these  
13 extraneous variables are relevant, I am suggesting the  
14 potential for impeding experiment over time. Not all  
15 animals have to be done at once. You can do a  
16 fraction of the study each time. All treatments  
17 appear at each time, though, obviously, not replicated  
18 quite as much knowing full well you're going to do  
19 this a multiple times. We often ask that multiple  
20 lots of product be tested, so the idea would be lots  
21 of product would be evaluated each time, a new batch  
22 of inoculate each time, new cage batteries each time

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1 and this way you could have enough animals that are of  
2 comparable ages that could come on to a study at one  
3 point and a sponsor could potentially manage the  
4 resources better. Next.

5 The big advantage to replicating over time  
6 is you can assess the overall reproducibility of the  
7 study. And with both the log reduction study and the  
8 two-group study, there will be variation of the  
9 initial inoculate. Reproducibility and time is a  
10 compromise because what we usually see here is  
11 reproducibility of clinical sites. It's just not  
12 feasible in this kind of study. These animals are in  
13 fairly specialized facilities when they're studied.

14 Data analysis; many of the journal  
15 articles in this area, because they involve small  
16 studies and lots of treatments are often presented in  
17 an exploratory context, but they do not present formal  
18 statistical analyses and by that I mean, you don't see  
19 P values past the significance and 95 percent  
20 confidence levels. It doesn't invalidate the value of  
21 the studies, but they're just not done. Valid  
22 scientific evidence, as I've indicated at the

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1 beginning, does require appropriate statistical  
2 analysis and we ask that the analysis be consistent  
3 with the study design. Next.

4 Sample sizes in a sample design. I'm  
5 going to consider a case of two groups, one control  
6 and one group that's exposed to disinfectant. And I'm  
7 going to consider an binary end point just to  
8 illustrate the point. There needs to be enough  
9 control animals to establish that inoculate be  
10 sufficiently deadly and enough treatment animals to  
11 say at least 99 percent will survive the disease and  
12 we're not wedded to this end point but this is one  
13 potential scenario that one could have. Next.

14 The numbers; one could potentially have  
15 two cages of animals each time to establish the  
16 inoculate is sufficiently infectious and you would  
17 expect 100 percent mortality within a given period of  
18 time. In the treatment group, one could potentially  
19 expect 100 percent survival, at which point the thing  
20 I will point out is even though you might observe 100  
21 percent survival, how sure you are that in the future  
22 100 percent will survive is very much tied to the

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1 sample size in the study. And so if you want to be  
2 able to say that even though I've observed 100 percent  
3 survival, I want to say in the future I'm pretty  
4 comfortable and confident that it's going to exceed 99  
5 percent. It turns out you actually need about 300  
6 animals in the absence of considering any cage effect  
7 at all. So we need to realize even with an all or  
8 nothing you may need a sample size in order to confirm  
9 for the future that this product is going to be  
10 successful. Next.

11 Precision of survival in this, you have 75  
12 cages and four animals, just the contrast with the  
13 dependence within a cage can do. Ninety-two percent  
14 survival. I selected it because it was a multiple of  
15 four. And no cage effects, even though you're  
16 observing 92 percent, you're going to see a confidence  
17 level that ranges anywhere from 88.3 to 94.8 percent.

18 And I've taken the extreme case where all the animals  
19 die within a cage or none die. The confidence level  
20 would then be determined by the number of cages rather  
21 than the number of animals and suddenly the confidence  
22 level get a bit wider. Obviously, in real life we'll

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1 see something in between but again, to just illustrate  
2 the concept, that even with 100 percent survival,  
3 which is obviously, an idea outcome, okay, with  
4 independence, the lower confidence bound is a bit  
5 higher than it would be with complete dependence  
6 because you have less information because of the cage,  
7 animals of the same cage not being totally independent  
8 in real life and we'll be observing something in the  
9 middle. Go on.

10 And time to event data, which could be  
11 survival or time to onset of symptoms, the sample size  
12 actually gets pretty complex by comparison. It's  
13 going to vary by the animal model, the source of  
14 prion, the survival or symptoms, whether you decide  
15 time until symptoms or time until death and how big an  
16 effect you want to see. It is enough that a mouse  
17 survives another week or do you want to quantify a  
18 magnitude effect that has relevance?

19 You would need preliminary data including  
20 meaning of survival due to completing causes, perhaps  
21 from a normal breeding colony, meaning of survival in  
22 control groups or groups in the case of a log

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1 reduction end point, meaning of survival in the group  
2 treated with the product would be needed but one would  
3 assume that a sponsor would have some preliminary data  
4 to support those. You still have the same  
5 considerations. You do want to consider lot-to-lot  
6 variation in both the design and analysis.

7 You might want to vary the amount of  
8 infectious material in the inoculate by virtually just  
9 preparing a new inoculate. Cage effects will matter  
10 and if the competing causes are frequent you're going  
11 to need a bigger sample size. Statistical efficiency  
12 is actually driven by the number of deaths due to  
13 prion disease. It's not the number of animals on  
14 test. Next.

15 So in conclusion, the details of the  
16 specific design will certainly vary with the animal  
17 model. Key sources of variation need to be considered  
18 in both the design and analysis. The design should  
19 consider experimental units and the study must be  
20 sized sufficiently to establish product effectiveness  
21 within an appropriate level of certainty. Thank you  
22 very much.

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1 CHAIRMAN EDMISTON: Thank you. Mr. Brown?

2 MR. BROWN: Good morning. My name is Ron  
3 Brown. I'm a Laboratory Intermediary for Biological  
4 Risk Assessment in CDRH Office of Science and  
5 Engineering Laboratories. I'd like to discuss the  
6 work that we've done to characterize the iatrogenic  
7 CJD risk when we process neurosurgical instruments.  
8 Next slide, please.

9 You heard Dr. Murphy mention earlier that  
10 there are various risk/benefit considerations that  
11 need to be taken into account when looking at the risk  
12 of these instruments. Specifically, what we've done  
13 is to assess the annual risk of iatrogenic CJD in the  
14 US in patients undergoing neurosurgery with  
15 reprocessed neurosurgical instruments. And I want to  
16 be very clear, we haven't considered the risk of CJD  
17 transmission from instruments that are used at  
18 extraneural sites that are either used for  
19 neurosurgery subsequently or used for general surgery.

20 Next slide.

21 By way of overview, I'd like to discuss  
22 the models that we used to estimate the risk, provide

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1 justification for the parameter values that we used in  
2 the model. I'm going to say this repeatedly  
3 throughout the presentation but I really want to  
4 underscore the uncertainty associated with many of  
5 these parameter values. And then finally, how do we  
6 assess the impact of the parameter values on the  
7 estimated risk.

8 Now, I've borrowed a slide from Dr.  
9 Mayhall in which she looked at the characteristics  
10 necessary to assess the risk of TSE transmission. And  
11 very simply, we want to look at the likelihood of a  
12 transmissible encounter or simply what's the  
13 probability of exposure to the patient. And then once  
14 that exposure has occurred, what's the availability of  
15 the TSE source or how much of that agent was actually  
16 transferred to the patient. And then finally we want  
17 to consider the infectivity of the material.

18 Now, in answering these questions, we want  
19 to use the paradigm that was established by the  
20 National Academy of Sciences primarily to look at  
21 chemical risk assessment, but I think it's entirely  
22 applicable here. And that approach involves four

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1 steps, the first of which is hazard identification,  
2 exposure assessment then, dose response assessment and  
3 then risk characterization. So in hazard  
4 identification we simply want to know can the CJ-  
5 infected material serve as a source for iatrogenic  
6 CJD.

7 Exposure assessment, as the name suggests,  
8 is how much of that material was the patient really  
9 exposed to. In the dose response assessment we want  
10 to take into account the infectivity of the material  
11 and risk characterization simply balances the exposure  
12 assessment and the dose response assessment. I'm not  
13 going to say too much about hazard identification  
14 because I think it's been covered in detail by my  
15 colleagues but it simply addresses the potential for  
16 the prion protein go cause the iatrogenic CJD. And in  
17 fact, as we heard earlier, there are several cases of  
18 iatrogenic CJD that have been reported in the  
19 literature.

20 Exposure assessment really the first phase  
21 is what's the probability of a patient being exposed  
22 to these contaminated devices. So we want to know

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1 what the number of neurosurgeries that are performed  
2 in the US every year is and what's the proportion of  
3 the population that's infected with CJD, actually more  
4 accurately, what's the pool of asymptomatic CJD  
5 patients. Once the exposure has occurred then, we  
6 want to look at how much of that material is  
7 transferred to the patient both before cleaning and  
8 afterwards and what's the efficiency of the routine  
9 cleaning and sterilization methods.

10 As I mentioned with dose response  
11 assessment, we're looking at the infectivity in the  
12 material represented as an intercerebral IC50. Now we  
13 have several assumptions that we're using in the  
14 model, the first of which is that there's a linear  
15 dose response assessment. So if there's a threshold  
16 here, this may be a conservative assumption. We're  
17 also assuming that all exposed individuals are  
18 vulnerable to the infection but we know that there are  
19 genetic variations that may make some patients more or  
20 less susceptible. Now, it's not clear the extent to  
21 which that effects, just the incubation period or the  
22 actual manifestation of the disease. Next slide,

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1 please.

2 Now, the model we're using is actually a  
3 very similar one and it's a simple one and it's  
4 similar to the one that our colleagues in the UK used  
5 in their assessment of vCJD infectivity on reprocessed  
6 surgical instruments. Next slide, please.

7 Now, we've used two approaches in solving  
8 this, one of which was a very simple deterministic  
9 approach in which we picked point estimates for each  
10 of the parameters and then we solved the model  
11 individually. So in doing that, we could only see one  
12 solution at a time but it's useful to ask what if  
13 questions. For example, we can keep all the  
14 parameters the same, change one and say, "What's the  
15 impact of the change in this one parameter going to  
16 have on the estimate of risk". We solve this equation  
17 in Excel and as I'll point out, we selected various  
18 defaults for the parameter values.

19 Alternately, we used a probablistic  
20 approach. Some of you may be familiar with the Monte  
21 Carlo method. It's consistent with that. What this  
22 approach does, it's a modeling approach and it

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1 repeatedly samples values from the probability  
2 distributions for each value. So for example, we have  
3 seven parameters in the model and there's uncertainty  
4 associated with each of those values. We can use  
5 blood pressure an example. The mean blood pressure,  
6 let's say in the population is 120/80, but we know  
7 that there's considerable variability in that  
8 population.

9 The same is true for these parameters as  
10 well. So what the model will do is go in  
11 independently and sample from those distributions for  
12 each of the parameters. What this does is it allows  
13 us to examine the aggregate uncertainties for all  
14 those parameters together and how that carries over  
15 into the uncertainties of the risk estimate. So to do  
16 this analysis, I used a software called a RiskAmp  
17 Monte Carlo Add-in for Excel.

18 Let me just spend a few minutes on the  
19 specific assumptions that we used for each of these  
20 parameter values starting with a number of  
21 neurosurgical procedures. We had data from both CDC  
22 and the open literature suggesting that there were

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1 about 100,000 surgeries conducted in the year 2000. If  
2 we scale that up at about four percent a year, as a  
3 default value we assumed 125,000 neurosurgeries in the  
4 US this year. That's actually one of our more  
5 certain parameter values. Next slide, please.

6 Unlike the following, there was a question  
7 earlier about the proportion of asymptomatic CJD in  
8 the US population. As my colleagues mentioned  
9 earlier, the annual incidents of sporadic CJD, not  
10 variant CJD in the US is about one in a million. And  
11 but I want to be very clear that the prevalence of  
12 subclinical disease is unknown. We're assuming a  
13 background rate of asymptomatic CJD for the model.  
14 The question is, how much higher. As a default value,  
15 we're assuming that the background of asymptomatic is  
16 about two-fold higher than the clinical disease.  
17 However, our colleagues in the Center for Biologics  
18 have assumed that the incidents can be as high as one  
19 in 100,000 in the US population.

20 Now, before I leave that slide, let me  
21 just point out in passing that we are aware that there  
22 was the one case of variant CJD in the US population,

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1 probably not from a domestic source. So we're not  
2 taking vCJD in to account explicitly in these risk  
3 calculations.

4 Again, there's considerable uncertainty  
5 that the tissue mass on the instrument borrowing the  
6 assumptions from our colleagues in the UK, with their  
7 assessment of vCJD transmission from iatrogenic use of  
8 devices, they assumed that there was 10 milligrams of  
9 tissue remaining on the instruments after use and  
10 about 20 instruments were used per neurological  
11 procedure. So that would give us an aggregate of  
12 about 200 milligrams of tissue that the patient might  
13 be exposed to. And the range that we'll use from our  
14 probabilistic sense is .1 to .5 grams remaining in  
15 aggregate on the tissues.

16 This is an area of considerable  
17 uncertainty as well. How much of that tissue is  
18 transferred to the patient after sterilization and  
19 cleaning. Our colleagues in the UK really assumed a  
20 very wide range from -- let me use the pointer here --  
21 essentially all the material being transferred to very  
22 little. But we're going to use the default assumption

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1 that 10 percent of that material is transferred upon  
2 use. And I believe later on this morning we'll hear  
3 in Mr. Hilderly's presentation the theory that  
4 material doesn't have to be transferred in order for  
5 infectivity to be transferred. That it's possible for  
6 just contact with the abnormal protein to occur. We  
7 did not explicitly account for that in this risk  
8 assessment. Next slide, please.

9 Now, we wanted to make some assumptions  
10 about how well routine cleaning removed the myoburden  
11 (phonetic). Typically when we're talking about the  
12 microbial myoburden, it's often assumed that routine  
13 cleaning will reduce microbial contamination by about  
14 four orders of magnitude. Based on the results of  
15 Alpha et al (phonetic) it seems like protein sticks to  
16 devices a little bit more actively. It's harder to  
17 get it off. Next slide, please.

18 However, the paper by Verjat et al  
19 suggests that on flat surfaces, you can remove up to  
20 five orders of magnitude of the protein. So in this  
21 case we're using protein as a surrogate from the  
22 remaining tissue. Now, you may remember the slides

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1 that Dr. Murphy showed, the different types of  
2 devices. For example, the brain scoops, those would  
3 probably have a flatter surface. We can expect to get  
4 more of the tissue off. Some of the other devices  
5 like the bone rogeur have a lot of nooks and crannies.

6 It's going to be harder to get that tissue off. So  
7 accordingly, we try to have a range of removal from  
8 just routine cleaning.

9 This is going to be a subject of, I'm  
10 sure, considerable discussion and perhaps controversy  
11 at the meeting today but we wanted to have some  
12 assumptions about the extent to which routine  
13 sterilization removed infectivity on devices. And  
14 here we defaulted to our -- the assumption that our  
15 colleagues in the UK used that routine sterilization  
16 reduces infectivity of prion protein by three to six  
17 logs and as a default we're going to assume four-log  
18 reduction.

19 So in aggregate when we take into account  
20 cleaning, which reduces infectivity by two logs, and  
21 sterilization four logs, as a default, we're assuming  
22 a six-log reduction in infectivity from just routine

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1 cleaning and disinfection, sterilization, excuse me.

2 Now as Dr. Murphy mentioned earlier,  
3 there's a limited range of tissue infectivity  
4 depending on the host and the specific prion. Again,  
5 we're going to default to the judgment of our  
6 colleagues in the UK and the assumption that they use,  
7 that for the asymptomatic case, that it's reasonable  
8 to assume 10<sup>8</sup> intercerebral ICID50s for gram of brain  
9 tissue for the -- again, for the subclinical disease.

10 And this is the justification for their assumption.

11 Now, I want to point out that one of the  
12 very early stages of this risk assessment, one thing  
13 that I haven't done is stratify for age. And we know  
14 because of the prolonged incubation period, the  
15 infectivity of tissue in older individuals may be  
16 higher than that for younger. I just haven't gotten  
17 around to that yet in this analysis.

18 So if we plug in those defaults and I've  
19 listed them here, into the very simple equation, we  
20 can see that the estimated annual risk of infections  
21 for iatrogenic CJD from the use of reprocessed  
22 neurosurgical instrument is about .25 infections per

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1 year. Now, you can see a couple of significant  
2 figures here but I want to dissuade you from thinking  
3 that there's any precision involved at all in this  
4 number because of the uncertainty in those parameter  
5 values. I think maybe the best way to look at this  
6 is, we estimate based on the assumptions that we've  
7 used that there are probably less than one infection  
8 per year from this source.

9 Now, this slide may be a little bit hard  
10 to read but let me just call your attention to the  
11 left column in which we look at log reduction in  
12 infectivity and again, as a default we've assumed six  
13 long reduction in infectivity and a starting  
14 infectivity on the tissue of  $10^8$  IC50, ICID50's per  
15 gram of tissue and that gives us that estimate of .25.

16 So since this is a very simple linear model, any  
17 changes to the input parameters are going to be  
18 reflected in the estimates of risk in a linear way.

19 So let's say that we were off on our  
20 assumptions of how well we can clean and disinfect and  
21 we can only get down to four log reduction of  
22 infectivity. Well, you can see what impact that would

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1 have on the estimates of risk here. Actually, in the  
2 risk assessment that I believe you got, we went  
3 through this exercise for each of the seven parameter  
4 values. Now, I mentioned that we used this  
5 probablistic approach. So using default values that  
6 is consistent with a uniform distribution, where you  
7 just pick one value, but we know for a lot of  
8 biological values, parameters, that there's a  
9 variability in the population.

10 So if it was a biological value, we might  
11 assume a normal or a log normal distribution. But we  
12 really don't have that information for the parameters  
13 that we've used in our risk assessment, so it's common  
14 in Monte Carlo analysis to just assume a triangular  
15 distribution, which is what we've done for this first  
16 draft of the risk assessment. Next slide.

17 It's a little bit harder to read again,  
18 but this slide just summarizes the defaults and the  
19 lower bound and upper bound values for each of the  
20 parameters in the model. So we used the model, we  
21 solved it 10,000 times, 10,000 iterations with those  
22 upper and lower defaults and these are the estimated

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