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UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MICROBIOLOGY DEVICES PANEL MEETING

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Thursday,

March 7, 2002

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The meeting was called to order at 10:36 a.m., in the Main Ballroom of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, by Michael L. Wilson, Panel Chair, presiding.

PRESENT:

DR. MICHAEL L. WILSON, Chairman  
DR. KATHLEEN G. BEAVIS, Member  
DR. MARGO A. SMITH, Member  
MS. STANLEY M. REYNOLDS, Member  
DR. CARMELITA U. TUAZON, Member  
DR. RONALD J. ZABRANSKY, Member  
DR. IRVING NACHAMKIN, Consultant  
DR. VALERIE L. NG, Consultant  
DR. L. BARTH RELLER, Consultant  
DR. LAURI D. THRUPP, Consultant

ALSO PRESENT:

DR. JOHN TICEHURST  
DR. ROXANNE SHIVELY  
MS. MARJORIE G. SHUMAN  
DR. ROSEMARY HUMES  
DR. J. EDWARD BROWN  
DR. JOHN W. EZZELL

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## P-R-O-C-E-E-D-I-N-G-S

(10:36 a.m.)

1  
2  
3 CHAIRMAN WILSON: I would like to call the  
4 panel to order. I am Dr. Michael Wilson, Panel Chair,  
5 and I would like to begin the meeting by going around  
6 the table and have all the panel members identify  
7 themselves and give their affiliations, and if we  
8 could start with you, Ron.

9 DR. ZABRANSKY: Ron Zabransky, I'm  
10 retired, and I was previously with the DA.

11 DR. THRUPP: Lauri Thrupp, University of  
12 California at Irvine.

13 DR. RELLER: Barth Reller, Duke University  
14 Medical Center.

15 DR. SMITH: Margo Smith, of the Washington  
16 Hospital Center.

17 CHAIRMAN WILSON: Again, I am Michael  
18 Wilson, from the Denver Health Medical Center, and the  
19 University of Colorado.

20 DR. BEAVIS: Kathleen Beavis, Cook County  
21 Hospital.

22 DR. NACHAMKIN: Irving Nachamkin, Hospital  
23 of the University of Pennsylvania, School of Medicine.

24 DR. NG: Valerie Ng, Department of  
25 Laboratory Medicine, San Francisco, California, and

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1 San Francisco General Hospital.

2 DR. TUAZON: Carmelita Tuazon, George  
3 Washington University Medical Center.

4 MR. REYNOLDS: Stanley Reynolds,  
5 Pennsylvania Department of Health, and Consumer  
6 Representative.

7 CHAIRMAN WILSON: Welcome. At this time,  
8 I would like to just turn the meeting over to Ms.  
9 Freddie Poole, who will read the conflict of interest  
10 statement and make other opening remarks.

11 MS. POOLE: Good morning. I will first  
12 read the conflict of interest statement for this  
13 meeting. The following announcement addresses  
14 conflict of interest issues associated with this  
15 meeting, and is made a part of the record to preclude  
16 even the appearance of an impropriety.

17 To determine if any conflict existed, the  
18 Agency reviewed the submitted agenda on all financial  
19 interests reported by the committee participants. The  
20 conflict of interest statute prohibits special  
21 government employees from participating in matters  
22 that could affect their or their employees' financial  
23 interest.

24 However, the agency has determined that  
25 participation of certain members and consultants, the

1 need for whose services outweighs the potential  
2 conflict of interest involved is in the best interest  
3 of the government.

4 We would like to note for the record that  
5 the agency took into consideration certain matters  
6 regarding Drs. Kathleen Beavis and Margo Smith. Each  
7 of these panelists reported current interests in firms  
8 and issues, but in matters not related to the topic  
9 for today's agenda.

10 The agency has determined, therefore, that  
11 they may participate fully in all deliberations. In  
12 the event that the discussions involve any other  
13 products or firms not already on the agenda, for which  
14 an FDA participant has a financial interest, the  
15 participant should excuse him or herself from such  
16 involvement, and the exclusion will be noted for the  
17 record.

18 With respect to all other participants, we  
19 ask that in the interest of fairness that all persons  
20 making statements or presentations disclose any  
21 current or previous financial involvement with any  
22 firm whose products they may wish to comment upon.

23 Some housekeeping matters. We would also  
24 ask that if anyone has a cell phone or a pager that  
25 has a sound emitting, if you could turn it off during

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1 these proceedings.

2 And under old business on October 12th and  
3 13th, this panel met to consider two PMAs and a  
4 510(k). On November 28th, the selection of  
5 QuantiFERON TB was approved, subject to the  
6 recommendations made by the panel at the meeting.

7 The sepsis and the toxin activity assay  
8 was sent a Not Approvable letter in concurrence with  
9 the recommendations made by the panel. And the  
10 OsMetech urinary tract infection analyzer was found  
11 substantially equivalent, but with restrictions for  
12 its use. Thank you.

13 CHAIRMAN WILSON: Thank you, Freddie. The  
14 new business for the new day is the discussion of the  
15 classification of pre-1976 products regarding bacillus  
16 anthracis and yersinia pestis.

17 I would like to remind everyone that these  
18 are not applications. What the purpose of the meeting  
19 today is for is to classify these devices that have  
20 never been previously classified. And that there are  
21 no submissions for this today.

22 I am going to start off with the  
23 presentation from the FDA by Ms. Roxanne Shively. I  
24 would like to ask all the panel members to hold their  
25 questions until after the presentation is through.

1           And I would also like to remind the  
2 audience that only members of the panel can ask  
3 questions of the speakers today. Roxanne.

4           DR. SHIVELY: Thank you, Dr. Wilson. Just  
5 a moment and we will get video and text up here.

6           (Brief Pause.)

7           DR. SHIVELY: Well, good morning, and we  
8 certainly and very greatly appreciate and welcome your  
9 collective knowledge and experience for this  
10 classification meeting.

11           The objective for today's meeting is for  
12 you to recommend an appropriate regulatory  
13 classification for pre-amendment products used to  
14 identify bacillus anthracis and yersinia pestis.

15           These products, when used in a clinical  
16 laboratory, aided in the diagnosis of human anthrax  
17 and plague. These products were marketed and labeled  
18 for intended use prior to May of 1976. We believe  
19 that these products may have been overlooked by the  
20 FDA when pre-amendment products were classified by a  
21 similar process in 1980.

22           These products were not in the DIFC  
23 manual, but rather were distributed primarily by  
24 public health laboratories and other specialty  
25 laboratories to other labs who were also performing

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1 tests on human specimens.

2 The plan today is to proceed through the  
3 complete classification process; first, for the  
4 bacillus products, and then for the yersinia pestis  
5 products.

6 For the bacillus products, the FDA will describe  
7 the three product types that were used pre-amendment.  
8 These include a specific bacteriophage, antibody  
9 conjugates, and antigens for antibody detection.  
10 Information about these products was obtained from  
11 published literature, both journal article reports and  
12 reference manuals.

13 FDA will also describe the risks  
14 associated with each of these product types and will  
15 reiterate the types of controls that can be applied.  
16 My presentation will not be long, and will highlight  
17 some of the information that was provided to you in  
18 the package sent to you before this meeting.

19 We hope that information was helpful in  
20 preparing for today. You will have opportunities to  
21 ask questions about the information presented, and  
22 then also for discussion of the issues addressed by  
23 the FDA questions.

24 And finally you will be asked to recommend  
25 a classification for each product type. I would like

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1 to note and emphasize that although these three  
2 product types are being presented together as a  
3 product class that has a common use, they can each be  
4 classified differently; that is, at a different level.

5 Just to remind you that the bacillus  
6 species are all spore-forming, gram-positive rods.  
7 The genus is an extensive taxonomic array with 50 or  
8 more species. Of these, two are clinically important:  
9 the bacillus anthracis and the bacillus cereus.

10 There are a few endemic areas of bacillus  
11 anthracis remaining in the United States, with very  
12 rare human anthrax. However, cutaneous anthrax is not  
13 uncommon in endemic areas worldwide.

14 Bacillus cereus causes a self-limiting  
15 gastrointestinal disease. Rarely, it can cause  
16 nongastrointestinal disease, particularly with IV drug  
17 users and immunosuppressed individuals, particularly  
18 following surgical procedures.

19 The laboratory identification of these  
20 organisms can be challenging. No one characteristic  
21 is sufficient to discriminate these species, either by  
22 morphology or biochemical characteristics from  
23 culture.

24 Differentiation of bacillus anthracis is  
25 important not only clinically, but for biosafety and

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1 public health purposes. As with other infectious  
2 diseases, the detection of antibodies may be useful  
3 retrospectively and for epidemiological information.

4 The first product in this group is a vial  
5 of specific bacterial virus that was used in a culture  
6 plating method to distinguish bacillus anthracis from  
7 bacillus cereus and other species.

8 This gamma phage reagent was originally  
9 developed by Dr. Cherry at CDC, and later distributed  
10 by CDC and other veterinary and public health  
11 laboratories.

12 The key article describing this reagent  
13 and use of the reagent is from 1955 by Brown and  
14 Cherry. Factors that were recorded to affect results  
15 using this reagent, and potentially could cause a  
16 false positive or negative results are the following:  
17 variant strains can behave differently; titer and  
18 stability are important for reliable performance; the  
19 media used; the length of incubation; and the inoculum  
20 density can affect results; as can the technologist's  
21 experience with interpreting lysis.

22 The next pre-amendments product is a vial  
23 of fluorescein-labeled antibody against bacillus  
24 anthracis that is used to microscopically visualize  
25 specific binding with cultured organisms or organisms

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1 in infected specimens.

2 This fluorescence provides presumptive  
3 evidence for identification of bacillus anthracis.  
4 There were various sources for hyperimmune antisera,  
5 preamendments, and the key publication is one from  
6 1959 by Cherry and Freeman.

7 This report was not sent to you earlier,  
8 but if you are interested in having it or looking  
9 through it, we will have it for you today, and that's  
10 why it is in yellow. There are a couple of other  
11 places throughout the presentation where I have put  
12 the text in yellow and that just denotes something new  
13 that wasn't already in your package.

14 Factors that could affect results using  
15 this reagent are that some of the capsular and cell  
16 surface antigens of bacillus anthracis are shared by  
17 other species.

18 Preparing high-titer antiserum in animals  
19 can be difficult and poses safety concerns. The spor-  
20 surface antigens are not species specific and this  
21 product is intended for us with vegetative cells.  
22 Growth conditions affect encapsulation, and inoculum  
23 density used can affect results.

24 The third product type in this group is a  
25 vial of antigens prepared from cell filtrates that is

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1 used to detect antibodies to bacillus anthracis in  
2 human serum.

3 These antibodies can be either anti-toxin  
4 or anti-capsular, or both. This reagent was  
5 originally used with an immunodiffusion method. At  
6 the time your panel packages were prepared, we didn't  
7 have much information on this product.

8 Thanks to colleagues who opened their  
9 files and shared their knowledge, we were able to  
10 retrieve a key article by Ray and Kadull from 1964,  
11 and this report described the use of a modified agar  
12 diffusion method with an antigen that was prepared  
13 from cultures of the Sterne strain.

14 Initially this reagent and method were  
15 used for determining serological responses to  
16 immunization, but were also applied to testing human  
17 sera from individuals with anthrax.

18 No cross-reactivity with sera from humans  
19 with brucellosis, influenza, listeriosis, and several  
20 other diseases was noted, and in using these antigens,  
21 the results were 94 percent reproducible, within plus  
22 or minus two dilutions.

23 The authors reported that the indirect or  
24 the inhibition method was 50 percent more sensitive  
25 than the direct method. They also showed that the

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1 reconstituted antigen preparations were stable for one  
2 month at minus 15 degrees.

3 This reagent was available in the United  
4 States, primarily from the U.S. Army Biological  
5 Laboratories. Factors that were reported to affect  
6 results were the purity of the antigen preparation,  
7 its concentration, and also prozone effects can impact  
8 on results.

9 And the endpoints can be quite subjective  
10 to read. Nonspecific reactivity can occur, and  
11 patients being tested could have an abrogated antibody  
12 response due to antibiotic treatment. This test is  
13 unable to differentiate recent from past infections,  
14 or prior vaccination.

15 I have a few historical and summary notes  
16 to finish with this product group. The antigen  
17 precipitin test, first described by Ascoli in 1911, is  
18 one of the oldest laboratory tests ever. It was used  
19 primarily for detecting bacillus anthracis antigens in  
20 animal tissues, and it is known not to be specific for  
21 bacillus anthracis.

22 But practically, it worked when used in  
23 certain situations and this Ascoli reagent was also  
24 commercially available worldwide.

25 Preamendment diagnostic laboratory testing

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1 was limited to specialized and public health  
2 laboratories. Reagents were developed and prepared in  
3 these laboratories, and distributed with other  
4 laboratories, both nationally and internationally.

5 As a final note, human anthrax disease is  
6 rare, and vaccination has successfully controlled the  
7 disease in animals. But to put things into  
8 perspective, now we have a list of critical biological  
9 agents, and bacillus anthracis is one of the high  
10 priority, or Category A agents, because it can be  
11 easily disseminated and can cause high mortality.

12 Other bacterial agents were classified in  
13 1980. That included another Category A agent,  
14 francisella tularensis, along with brucella  
15 pseudomonas and rickettsia that are Category B agents.

16 Please note that these are bacterial  
17 agents. As you know, viral agents are also on the  
18 critical agent list. As you learned this morning in  
19 training, products classification is based on assessed  
20 risks and level of controls that can mitigate those  
21 risks.

22 The risks for in vitro diagnostic are  
23 those that are associated with misdiagnosis and  
24 epidemiological misinformation due to false positives  
25 or false negative results.

1                   Controls under FDA regulations can be  
2 general or can include special controls. General  
3 controls include prohibition against adulterated or  
4 misbranded devices; premarket notification  
5 requirements; banned devices; good manufacturing  
6 practices; registration of manufacturing facilities;  
7 listing of device types; labeling in accordance with  
8 809.10(b); record keeping, and then repair,  
9 replacement, and refund practices by a company.

10                   The types of special controls include  
11 performance standards of various types; discretionary  
12 post-market surveillance, if the FDA determines that  
13 it is necessary to protect public health or provide  
14 safety and effectiveness data.

15                   Guidances can also be developed and  
16 disseminated. Guidances can address things such as  
17 requirements for clinical data in a 510(k), or  
18 specific labeling content regarding indications for  
19 use, instructions for use, contraindications,  
20 warnings, precautions, or adverse effects.

21                   Another category of special controls is a  
22 very open-ended type, and these are recommendations  
23 and other appropriate actions. This is a very  
24 flexible tool. Examples of this type of special  
25 control would be special labeling, or restrictions on

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1 sale, distribution, and use of the product.

2 I would like to remind you that currently  
3 there are some guidances and laws that already apply  
4 to tests performed on or with bacillus anthracis.  
5 These include organism-specific practice guides  
6 promulgated by CDC; local, state, and national  
7 reporting requirements; biosafety guidelines; and  
8 finally the Select Agents Rule that limits quality  
9 control materials to vaccine strains.

10 Thank you for your attention, and Dr.  
11 Wilson, is there time for questions now, or should we  
12 save those until later?

13 CHAIRMAN WILSON: I think there is time  
14 for a few questions. So at this time I would like to  
15 open up the discussion to the panel members, and the  
16 questions for Ms. Shively.

17 DR. SHIVELY: If anyone has any questions  
18 about the information I have presented, I can take  
19 them now.

20 CHAIRMAN WILSON: Carmelita.

21 DR. TUAZON: Do we have any information as  
22 to the problems with the use of these agents?

23 DR. SHIVELY: That is a question that  
24 perhaps can be directed to some of the experts in the  
25 audience who are in attendance. Would we like to do

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1 that now or at a later time?

2 CHAIRMAN WILSON: Sure. No, we can do  
3 that now. If Drs. Brown and Ezzell would like to come  
4 up, they could possibly answer some of these questions  
5 for us.

6 DR. EZZELL: I am John Ezzell from  
7 USAMRIID. I think the question has to do with which  
8 of the assays, and probably any of these in general?

9 DR. SHIVELY: Those that have been  
10 enumerated.

11 DR. EZZELL: With respect to the gamma  
12 phage we have formed into the bacteriophage mode that  
13 Paul presented; the isolates are dried and cultured in  
14 original clinical material, that those cases we look  
15 at isolates with regard to -- we have not seen any  
16 false positive or false negative results.

17 And there may be variabilities in how --  
18 in the amount of inoculant. Now, if you look at the  
19 bacilli that are not normally associated with clinical  
20 materials, we have found on occasion very little of  
21 other organisms or bacilli that may have a reaction to  
22 primary bacillus.

23 And we have seen very few false positives  
24 with bacillus, but in that case the B. cereus strains  
25 are also clearly different shapes than types that are

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1 hemolytic, and most strains are not. And so we have  
2 other bacteria that can be used to differentiate.

3 So the problems with the gamma phage with  
4 the indication of these clinical isotopes have been  
5 very few, and have not created a problem.

6 CHAIRMAN WILSON: Mr. Reynolds.

7 MR. REYNOLDS: Is the gamma phage test  
8 meant to be a stand-alone test, or is this supposed to  
9 be interpreted as part of a battery of tests?

10 DR. EZZELL: It should be used in  
11 conjunction with other tests, and especially in the  
12 case of clinical samples, and you are going to be  
13 looking for the lumping of a colony -- that's one of  
14 the criteria, you're looking for a colony, and that is  
15 another one criteria -- in the gamma phage.

16 But we did not depend totally on this  
17 gamma phage method, there are other methods that go  
18 along with that. There may be clinical presentations,  
19 and it is not a stand alone test.

20 CHAIRMAN WILSON: Dr. Zabransky.

21 DR. ZABRANSKY: Regarding any of these  
22 reagents, the antigens, the antibodies, or the gamma  
23 phage, are they available commercially, or are they  
24 only available through agencies such as CDC and  
25 USAMRIID?

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1 DR. EZZELL: Right now they are only  
2 available through CDC.

3 CHAIRMAN WILSON: Dr. Thrupp.

4 DR. THRUPP: I was going to ask along the  
5 same lines. Does CDC and USAMRIID each produce them  
6 for distribution, or does CDC get theirs from you?

7 DR. EZZELL: Initially the CDC got them --  
8 they had originally performed -- in the case of the  
9 gamma phage. I do know that they have prepared a lot  
10 on their own. I have not seen the performance  
11 characteristics of this latest lot that they produced,  
12 but until recently most of the gamma phage that has  
13 been distributed was coming through from our  
14 laboratory, and they are provided to them under  
15 perfect controls.

16 DR. THRUPP: These questions could apply  
17 separately to the phage and to each of the tests, but  
18 you answering in general terms is helpful. In some of  
19 the papers or in some of the background data in the  
20 old studies, there were some problems with phage  
21 stability, for example, and stability with freezing  
22 and thawing.

23 DR. EZZELL: Right.

24 DR. THRUPP: And so the question would be  
25 obviously that they have not been a high use reagent,

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1 but they have been available over these last 30 or  
2 more years.

3 DR. EZZELL: Right.

4 DR. THRUPP: Have these kind of problems  
5 that were documented in the original papers been a  
6 continuing issue, or would you anticipate that there  
7 are going to be continuing problems if the use of  
8 these were to be expanded?

9 DR. EZZELL: What we have found, and one  
10 reason that we have been one of the producers of the  
11 gamma phage for CDC is that we looked at gamma phage  
12 produced using different strains of B. anthracis.

13 And what we found is that we have one  
14 strain which was originally identified years ago by  
15 CDC as CDC 684, and it identifies originally the  
16 bacillus megaterium type strain.

17 This strain has been subsequently found to  
18 have some unusual checklists, but it is a B. anthracis  
19 strain, and it is avirulent, but the gamma phage that  
20 we produced, and the gamma phage used in this  
21 particular strain, that phage is very stable.

22 We have had suspensions of this phage that  
23 we keep refrigerated. We do not freeze our phage,  
24 because freezing the phage does destroy the phage as  
25 it causes a dramatic drop in reactivity.

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1           So what we have found is that by producing  
2           the gamma phage with this particular strain that the  
3           phage is stable and we have lots that we have held for  
4           5 years and are still viable, and still produce.

5           And that is another thing, too. We do not  
6           run any gamma phage assay without running a perfect  
7           control. And we use the Pasteur, the old Pasteur  
8           vaccine strains, as our positive control, and that is  
9           run every time we run this assay.

10          So that is another assurance that the  
11          phage is performing properly.

12          CHAIRMAN WILSON: Dr. Zabransky.

13          DR. ZABRANSKY: Now, this B. meg. strain,  
14          this is not controlled like the anthrax strain then?

15          DR. EZZELL: Well, it is not megaterium.  
16          It is actually a B. anthracis. I and some others have  
17          assured --

18          DR. ZABRANSKY: Well, if I or any other  
19          company was going to set up a situation where I wanted  
20          to produce, I would have to get a hold of the other  
21          appropriate anthrax strain in order to propagate this.

22          DR. EZZELL: Yes, sir.

23          DR. ZABRANSKY: Which is controlled under  
24          the special agents rules.

25          DR. EZZELL: Right. But it is a virulent

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1 strain, but yes, you are correct that it is  
2 controlled. But we have tried to produce these under  
3 some restraints that were not controlled, and those  
4 strains and that phage are not stable either under a  
5 vaccine strain, or a --

6 CHAIRMAN WILSON: Dr. Reller.

7 DR. RELLER: I would like to ask Roxanne  
8 Shively, yourself, or anyone who would have this  
9 information -- when you presented the types of special  
10 controls, and then the next slide was other  
11 considerations, and especially the practice  
12 guidelines, and the quality control limits to select  
13 agents rule, are there currently in place other  
14 regulations that, in effect, already impose special  
15 controls having to do with distribution, for example,  
16 of these?

17 I mean, you could have as a special  
18 consideration restrictions on sale, distribution, or  
19 use, but are there already restrictions on  
20 distribution and use, based on CDC or other  
21 regulations? Do you follow the question?

22 DR. GUTMAN: I will take a stab at it.  
23 This is Dr. Gutman. As far as I know, there are not  
24 regulations in place that would restrict the sale of  
25 this product. There are requirements in place that if

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1 this product were going to be commercially distributed  
2 that it would have to knock at FDA's door, unless it  
3 was being distributed under investigational protocol,  
4 in which case, depending on how the investigation was  
5 set up, it might still have to knock at FDA's door.

6 And the issue at hand is that without a  
7 classification, when it comes knocking at the door, it  
8 comes as a Class III product, and would be a PMA.  
9 That would be true whether it was a commercial venture  
10 or distributing it, or frankly if anybody were  
11 distributing it.

12 So the other considerations are the  
13 contacts that could be cited in the guidance packs, or  
14 cited in the classification, and I don't know whether  
15 their status can be formalized, and they are helpful.

16 But in terms of an actual regulation that  
17 would preclude distribution, we would need to develop  
18 that off of this classification if that were the  
19 recommendation of this panel.

20 DR. RELER: Just as a follow-up question.  
21 One of the options for the panel would be to recommend  
22 restricted distribution, correct?

23 DR. GUTMAN: Absolutely. Of course.

24 DR. RELER: I would like to ask an open-  
25 ended question. Given, at least in my view, the

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1 importance of the clinical picture, the communication  
2 with the laboratory, and putting those pieces together  
3 in the identification of this agent, and we will come  
4 to this again with yersinia pestis, is there any  
5 reason to have clinical laboratories, commercial  
6 laboratories, have especially the gamma phage reagent.  
7 I mean, we could take them individually, but is there  
8 any need to have this available outside of public  
9 health laboratories?

10 DR. EZZELL: May I address that question?  
11 One of the problems that we are seeing now is that, in  
12 some of the Level A labs within the laboratory  
13 response network, hospital labs, that when people are  
14 seeing sometimes non-hemolytic bacilli coming up on  
15 blood cultures or in other types of isolations, that  
16 there is a number of individuals that get cause for  
17 alarm.

18 And they have no other mechanism other  
19 than to send it to a level B laboratory to confirm  
20 whether or not this is really a B. anthracis, and a  
21 number of these laboratories are very inexperienced,  
22 and the first time they see something, they are not  
23 really sure if it is a B. anthracis or not.

24 And last week I was speaking out in  
25 California, the California Public Health Department,

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1 and Jim Snyder, who has been very active to address  
2 some of the needs of the level A labs, one of the  
3 things that we see is a crying need for some sort of  
4 way that the level A labs or hospital labs, to have  
5 somebody do a quick screen on some of these isolates  
6 that are not having to run them up the chain, so to  
7 speak.

8 So one thing I had thought about was that  
9 if we can make these available to the hospital  
10 laboratories when they are doing routine screening,  
11 this would give them an added level of comfort that  
12 they don't have an anthrax case on their hands.

13 DR. RELLER: Exactly. So it seems to me  
14 -- well, when you do this case test, and given some of  
15 the pitfalls with running a control strain, is this  
16 what you would want to put in the hands of an  
17 inexperienced laboratory that has no capacity or  
18 doesn't correlate the clinical situation with the  
19 laboratory.

20 And because of their inexperience, you are  
21 going to put gamma phage there without controls or  
22 with controls, which would require or raises grave  
23 questions in my mind.

24 DR. EZZELL: Yes, I understand that, and  
25 one of the duties of a level B laboratory in each

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1 state is to train level A laboratories. So I do not  
2 think this gamma phage should go in any laboratory  
3 without the proper training and documentation, and  
4 that somehow there be some sort of proficiency testing  
5 involved.

6 And that is a whole another avenue that  
7 needs to be opened up, and how do we do proficiency  
8 testing on some of these threat agents. But in the  
9 case of the -- I firmly feel that there should be some  
10 sort of other test that someone can use in a level A  
11 laboratory other than, let's say, I have a non-  
12 hemolytic ground vessel looking colony, and what do I  
13 do with this.

14 And let's say at least at the laboratory  
15 level that there should be some sort of mechanism,  
16 that that would be some other test that they can do  
17 and that would help them, but those are my personal  
18 views on that.

19 But that is where I see or feel a number  
20 of problems across the country where people are  
21 running into problems at these Level A laboratories.

22 CHAIRMAN WILSON: Dr. Thrupp.

23 DR. THRUPP: I was going to mention the  
24 same point that Dr. Reller just raised; that, yes, it  
25 sounds like a nice idea to have a test available, but

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1 when you are dealing with inexperienced laboratories,  
2 and inexperienced in the use of these, number one; and  
3 number two, with hopefully an extremely low prevalence  
4 organism, their experience in handling them is going  
5 to be extremely limited.

6 And that is a hazard, and in the past we  
7 have had problems with those kinds of situations, and  
8 this is a very clinical-type thing. So I would echo  
9 Dr. Reller's caution.

10 But I was going to say that you nicely  
11 summarized for us the history of the gamma phage  
12 reagent. I wonder if you would be good enough to  
13 summarize the availability over the many years, and  
14 the history of what is happening with this production,  
15 distribution, and utilization of the fluorescent  
16 antibody, and of the antigen preparations.

17 DR. EZZELL: The fluorescent antibody  
18 assay was originally geared towards the capsule of B.  
19 anthracis, and this was a number of laboratories many  
20 years ago.

21 George Rikus and some of the other  
22 laboratories were looking at and had developed -- and  
23 also through CDC, as well, a fluorescent antibody that  
24 was to detect the capsule.

25 Those reagents for many years were largely

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1           unavailable or through a very limited availability  
2           through CDC.       More recently our laboratory  
3           reinvestigated and looked at capsule along with  
4           another antigen that was developed around 1988, which  
5           we published papers on this, which was polysaccharide,  
6           which was described back in the '50s and '60s by a  
7           number of other laboratories.

8                        But those two fluorescent antibodies have  
9           been made available more recently through CDC, and one  
10          which is towards capsule, and which is historically  
11          the antigen that we have used or been used mostly in  
12          clinical samples to demonstrate this particular  
13          capsule around encapsular bacilli in the blood.

14                       But a polysaccharide assay is one of the  
15          more recent developments, and it only has occurred  
16          since 1988. We have made both of these antibodies  
17          available to CDC as part of the laboratory response  
18          network, and they are stored there.

19                       DR. THRUPP: And so both CDC and USAMRIID  
20          have both of these preparations?

21                       DR. EZZELL: Yes, sir.

22                       DR. THRUPP: And I don't recall whether  
23          any of the papers that we were presented with present  
24          data on comparison between the two?

25                       DR. EZZELL: Well, we have to use both of

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1 these antibodies together in conjunction. They are  
2 bacilli, and on culture, you can have some of the  
3 bacillus strains and a few other strains that will  
4 produce a capsule very similar to that of B.  
5 anthracis.

6 And also there is the polysaccharide, and  
7 we have to see the polysaccharide in the B-series  
8 strains as well. But we take both of these antigens  
9 together and there we have never seen another bacillus  
10 other than B. anthracis that will come up positive for  
11 both of those.

12 So we use those in conjunction with each  
13 other, and that is the basis of that assay.

14 DR. THRUPP: Do you want to comment on  
15 stability and how carefully they would have to be  
16 titered or should we come back to those later?

17 DR. BROWN: We didn't come prepared today  
18 to make a presentation on the specifics of our assays.  
19 We are willing to give as much information as we can,  
20 and understand that it is based on our recollections.  
21 But I just wanted to jump back to another point, and  
22 that was the question over here.

23 I am Ed Brown of USAMRIID also, and we are  
24 not representing the CDC, and we did not intend to  
25 distribute any of these reagents separately. The CDC

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1 has the responsibility for the domestic bioterrorism  
2 response.

3 And the intent as I understand it is that  
4 military labs will also get their reagents from the  
5 CDC. The CDC will be the sole source.

6 DR. EZZELL: The CDC is and will be  
7 producing them.

8 DR. BROWN: That is my understanding.

9 DR. GUTMAN: And let me point out that the  
10 basis of the classification is actually on the  
11 products that were out, and actually that Roxanne  
12 described, prior to the passage of the law.

13 The fact that those were out gives you the  
14 freedom to consider classifying these as a two, or as  
15 a three, or as a one, or whatever you should choose.  
16 And while the information on subsequent products  
17 certainly isn't irrelevant, and while the class path,  
18 if you decide to make this a Class II, there is the  
19 ability to extrapolate from the specific or the  
20 general specific kinds of claims that the relevant  
21 starting point, focal point, which is how comfortable  
22 you are having this grounded in these pre-amendment  
23 devices that we have been able to identify.

24 CHAIRMAN WILSON: Dr. Nachamkin.

25 DR. NACHAMKIN: And what about the antigen

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1 preparation and looking for antibodies? Is that also  
2 USAMRIID or is that CDC?

3 DR. EZZELL: That originally was USAMRIID,  
4 and then we have been working with CDC and we have  
5 sent our cell reagents down to CDC, and they are now  
6 going to be producing this test on their own.

7 I also go back to the antibodies, and the  
8 gamma phage. When the laboratory response network  
9 began, USAMRIID was designated, along with CDC, as the  
10 only two level B laboratories. And we are a member of  
11 the LREN.

12 As a member, we provided reagents and  
13 helped CDC develop their anthrax capability as far as  
14 reagents. And we provided those reagents initially.  
15 The CDC has now taken on that and they are working for  
16 anybody.

17 They are working with Cook, Art, and  
18 Perry, and also with their own laboratories down there  
19 to produce these reagents on their own. But we  
20 initially provided reagents.

21 CHAIRMAN WILSON: Dr. Nachamkin.

22 DR. NACHAMKIN: If somebody could just  
23 clarify this. The classification of this product or  
24 these group of products, and the yersinia products  
25 that we are going to consider this afternoon, that

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1 applies to commercial development of those reagents  
2 for sale to laboratories; it doesn't apply to, for  
3 example, CDC reagents. Is that correct?

4 I mean, they can produce anything they  
5 want and distribute them without --

6 DR. GUTMAN: Well, that actually is not  
7 correct. It theoretically applies to everyone who is  
8 commercially distributing these products. So it does  
9 apply to CDC.

10 DR. NACHAMKIN: Well, CDC has been  
11 distributing reagents for many, many years to  
12 laboratories. I wasn't aware that they were under any  
13 restrictions whatsoever.

14 DR. GUTMAN: Well, there is the tension  
15 between public health missions here and the FDA has  
16 certainly not intervened to block that flow of  
17 reagents, but frankly it is at the edge.

18 DR. NACHAMKIN: So if we classify this as  
19 a Class II device, CDC will have to adhere to that?

20 DR. GUTMAN: And if you classify it as a  
21 Class III, they would have to adhere to that, and to  
22 a Class I, and they would have to adhere to that.

23 DR. BROWN: Let me just make a summary  
24 comment, I guess. Having compared data with the  
25 people from the CDC, and looking at our experience

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1 over the following winter, and in what you might  
2 consider worst-case situations, we are not ready to  
3 present it today.

4 But we think there is strong evidence that  
5 these tests fall well within a Class I classification  
6 with the appropriate positive-negative controls, and  
7 the other general restrictions and controls that apply  
8 to Class I. So that would be our perspective.

9 CHAIRMAN WILSON: Dr. Beavis.

10 DR. BEAVIS: Yeah, the reagent was used  
11 for a positive control was mentioned, and what do you  
12 use for a negative control, and what has been your  
13 success or failure rate of the reagent, in terms of  
14 its control?

15 DR. EZZELL: With respect to the gamma  
16 phage, the negative control is a B. cereus strain, and  
17 obviously the positive control is the B. anthracis  
18 strain, and there is no limitation on its distribution  
19 to the laboratories.

20 DR. BEAVIS: How frequently does the QC  
21 fail when it is run?

22 DR. EZZELL: I have never experienced a  
23 failing.

24 DR. BEAVIS: Thank you.

25 DR. BROWN: Again, we would like a chance

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1 to bring that data forward to the FDA. Now we are in  
2 the process of putting together a submission, and  
3 hopefully a 510(k).

4 CHAIRMAN WILSON: Mr. Reynolds. Both Dr.  
5 Reller and Dr. Thrupp brought up the question of this  
6 being used in a level A laboratory, and I know that  
7 currently CDC only provides these reagents in Level B  
8 and C laboratories in the laboratory response network.

9 And at least in Pennsylvania, it is our  
10 feeling that we want Level A laboratories handling any  
11 of these potential organisms as little as possible.  
12 What recommendation, if any, if these reagents were  
13 made available at the Level A laboratories with people  
14 who had not had the experience in interpreting some of  
15 these objective tests that they would be looking at,  
16 would you have that these would be referred up the  
17 ladder even if you got a rule out result?

18 DR. BROWN: I personally would rather not  
19 answer that question, because it gets into the realm  
20 of deciding CDC's policy for CDC. That question would  
21 need to be addressed to them, if I could beg off a  
22 bit. John may want to give his own personal opinion.

23 DR. EZZELL: I tend to agree that we  
24 probably should not be speaking on behalf of the CDC.  
25 These are certainly -- the only test that I would

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1 consider moving any of these tests to a level A  
2 laboratory would be the gamma phage, and once again  
3 because I have been hearing from across the country  
4 the number of laboratories that have seen strains that  
5 they are very concerned about at the local level.

6 B. anthracis on culture, when you're  
7 working in a biological safety cabinet is an actual  
8 Level II agent that we have handled clinically. So,  
9 safety-wise, I don't see a problem there.

10 But I do -- but as I said, I have been  
11 working and talking with some of the people, like Jim  
12 Snyder, and others, trying to address some of these  
13 issues and where some of the labs have paranoia or  
14 whatever it is, and they are really concerned, and it  
15 would be nice if we had some mechanism so we can add  
16 one more thing at the local level to give them some  
17 sort of warm fuzzy feeling about whether or not this  
18 is B. anthracis or not before they try to move stuff  
19 up to the next level laboratory.

20 CHAIRMAN WILSON: Okay. Dr. Reller.

21 DR. RELLER: What is the problem with  
22 having a responsive public health network, where if I  
23 had an isolate that I had a question about, I would  
24 send it to Stan Reynolds. You know, if I were in a  
25 small laboratory in Pennsylvania.

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1                   And he would have the resources, as other  
2 public health laboratories, or New York City, to do  
3 the job swiftly, and communicate back to me rapidly to  
4 assuage my concerns, having first had access to  
5 infectious disease consultants who would be able to  
6 work with me, and that may have averted most of the  
7 ones that I would have to send to Mr. Reynolds in the  
8 first place.

9                   DR. BROWN: Well, I agree, and that is the  
10 way it is being handled now, that they are moving  
11 rapidly as possible, and moving these isolates over  
12 and consulting with the level B laboratory that they  
13 respond to.

14                   And it may be just a matter of certain  
15 laboratories getting more used to trying to refer  
16 these up the chain, and having to maintain these  
17 immediate contacts.

18                   The reason that I brought up the thing  
19 about the gamma phage is this possibility of one way  
20 to help these laboratories, because some of these  
21 laboratories have very good rapport with their  
22 laboratories that are immediately above them at the  
23 public health level that can answer these questions  
24 pretty fast.

25                   CHAIRMAN WILSON: Dr. Tuazon.

1 DR. TUAZON: I would just like to raise  
2 some issues about the differentiation between the anthrax  
3 and the B. bacillus. I think in clinical settings it  
4 presents very differently, but when you look at the  
5 culture, the important differentiation is in the B.  
6 cereus, and it is seen very differently in terms of  
7 the choice of the antibiotic.

8 But at that level, I think you already  
9 have your antimicrobial susceptibility, and the  
10 clinician would make the decision whether the patient  
11 should be treated for presumptive anthrax infection or  
12 presumptive bacillus cereus infection.

13 But my question is what is the level of  
14 the usage of this particular test in the last five  
15 years? I mean, how many cases have been referred to  
16 you for identification and differentiation?

17 DR. BROWN: Differentiating bacillus  
18 cereus with bacillus anthracis?

19 DR. TUAZON: In general, your gamma phage,  
20 your antibody, how many have you done in the last five  
21 years?

22 DR. BROWN: Well, since the middle of  
23 October, we have done quite a few.

24 DR. EZZELL: As far as clinical samples,  
25 we have had several outbreaks where we have had

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1 isolates that came to us from an occasional cutaneous  
2 anthrax case, we had one down in North Carolina.  
3 There have been actually very few cases that have been  
4 referred to us as far as isolates go in clinical  
5 samples.

6 Most of our isolates have come more from  
7 environmental type samples, and we would use the gamma  
8 phage here, once again taking or having the isolated  
9 organism and using gamma phage as a screening  
10 mechanism for this.

11 What we see, and from what I am hearing  
12 from the clinical laboratories, they have more of a  
13 problem when they get into like the megaterium type  
14 strain. B. cereus is a hemolytic strain that is  
15 very -- you know, usually works very nice with  
16 hemolysis, and typically that is not a problem.

17 It is used as a control here in this case,  
18 because of this being related to B. anthracis, but  
19 from what we have heard, it has been more of a problem  
20 with B. megaterium strains, and people question is  
21 this really B. anthracis or megaterium.

22 But I think also taking into consideration  
23 as you mentioned earlier that when the clinical  
24 picture is taken into consideration, most of these  
25 issues are probably worked out between the physician

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1 and the laboratory, and ruled out pretty fast in that  
2 regard.

3 CHAIRMAN WILSON: Dr. Zabransky.

4 DR. ZABRANSKY: I don't know if anybody  
5 has the answer to this question, but how do the  
6 veterinary labs fit into this picture regarding the  
7 CDC and the guidance they have provided us on  
8 reporting and so forth, and how would veterinary labs  
9 be involved with using these reagents for testing?

10 DR. EZZELL: Well, certainly I think  
11 something is still being worked out about health and  
12 doing animal surveillance, and this is an issue that  
13 has occurred more and more, especially with the USDA  
14 labs.

15 Linda Kelly has been working with some of  
16 these issues, and I think that some of these may be  
17 made available in the future, especially for a case of  
18 agricultural bioterrorism issues, and I think these  
19 are things that we will soon be seeing future  
20 interaction between these two different groups.

21 And to deal not only with human disease,  
22 but also animal disease, and some of the common uses  
23 of these for both, and freedom from either source.

24 CHAIRMAN WILSON: Dr. Gutman, this center  
25 though does not regulate products intended for

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1 veterinarian use does it?

2 DR. GUTMAN: That's correct. I am  
3 embarrassed to say I am not even sure exactly what  
4 statutes and regulations apply to that universe.

5 CHAIRMAN WILSON: Any other questions?

6 DR. BROWN: Let me just point out that in  
7 terms of our vision for an indication for a use  
8 statement would be on isolate colonies that are gram-  
9 positive, and hemolysin-negative, and have a  
10 suspicious colony morphology, that would be the target  
11 that the gamma phage or the DFA would be applied to.

12 So I am not formally trained as a  
13 microbiologist as Dr. Ezzell tells me all the time,  
14 but I think that is really going to cut down the  
15 population of suspect colonies that are to be  
16 submitted to the test, and decrease the possibility  
17 that it is going to be used in an incorrect manner.

18 I would just follow up with the third  
19 category, the antigens for antibody testing. We were  
20 trying to think where that might be applied, and Dr.  
21 Ezzell's idea was -- and it is just speculation on our  
22 part, but it would be looking at antibody levels, and  
23 trying to resolve a case of cutaneous anthrax and to  
24 make a definitive diagnosis.

25 So I think that where that might be used

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1 in a clinical setting is going to be very limited, but  
2 I would say, in terms of an assay to measure antibody  
3 levels, USAMRIID developed and validated IGG, and  
4 ELIZA to detect IGG, and this was in support of the  
5 Bioport vaccine effort.

6 And that data was put on a master file  
7 with the receiver, and now has been picked up by the  
8 CDC, and as Dr. Ezzell mentioned in support of their  
9 effort towards an anthrax vaccine.

10 CHAIRMAN WILSON: Dr. Thrupp.

11 DR. THRUPP: As a matter of information  
12 concerning the use of the antigen preparations for  
13 epidemiologic purposes, which could become relevant,  
14 does anybody know or can someone remind me -- in the  
15 Sverdlovsk Russian epidemic, my recollection was that  
16 they used antibody determinations to help determine  
17 the degree of the spread.

18 Was that using the same kind of reagent or  
19 does anybody know how they did that?

20 DR. BROWN: I don't have any data as to  
21 how they did that.

22 CHAIRMAN WILSON: I have a question for  
23 Dr. Ezzell. Given the emergence of newer molecular-  
24 based technologies, do you foresee a point at which  
25 the gamma phage will no longer be necessary or

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1 relevant, or do you see a future role for those  
2 products?

3 DR. EZZELL: I think it depends on the  
4 laboratory capability where these tests are being  
5 performed. We use PCR routinely in a number of  
6 laboratories, or certainly the PCR capability  
7 is being distributed to a number of level B  
8 laboratories through the LRN. I foresee the gamma  
9 phage still being used as a quick-screen assay.

10 And the gamma phage really -- and  
11 depending on how rapidly the organism grows that we  
12 have seen positive results within about 4 hours, and  
13 the quadrant of the plate in the gamma phage, and we  
14 have seen clear zones where there is a dull gray  
15 growth coming up within 4 to 5 hours.

16 And so that is still a fairly rapid assay,  
17 but I still see gamma phage as having a future role.  
18 As far as the FA, I don't know how widespread this is  
19 ultimately going to become, and certainly it is a  
20 little more involved with the FA, at least as to how  
21 it is being performed now.

22 But as far as the gamma phage part, I  
23 think that the gamma phage is still a very potent and  
24 powerful technique, and it should probably be around  
25 for a number of years.

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1                   But with the molecular assays becoming  
2 more and more easy, and more and more available to  
3 different laboratories, I foresee and I would predict  
4 that down the road we are going to see molecular  
5 assays being used in some cases for identification.

6                   CHAIRMAN WILSON:     Thank you.     Dr.  
7 Nachamkin.

8                   DR. NACHAMKIN:    Do you know if the FA  
9 reagent has been used at all to detect anthracis in  
10 tissues?  Do you have any data on that?

11                  DR. EZZELL:    Yes.  We have performed some  
12 assays on tissues that we have received from animals  
13 that we have done postmortems on, and we have had  
14 animals that have died in certain areas, and we have  
15 used the FAs to detect these antigens in tissues.

16                  DR. NACHAMKIN:  So it would seem that that  
17 might be more likely used for an FA reagent than maybe  
18 for organism identification?

19                  DR. EZZELL:    Yes.  In some cases, right,  
20 we have used it, and especially in tissues where some  
21 necrosis has occurred, and where we have had animals  
22 out for a number of days and using these reagents to  
23 detect antigens in the blood or in tissue.

24                  CHAIRMAN WILSON:  Okay.  We have time for  
25 one or two more questions.  Okay.  Thank you, Drs.

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1 Brown and Dr. Ezzell. At this point, I would like to  
2 move to the open public hearing.

3 Public attendees who have contacted the  
4 executive secretary prior to the meeting may address  
5 the panel and present information relevant to the  
6 unclassified pre-amendment devices.

7 And I would ask any of the speakers to  
8 state whether or not they have any financial  
9 involvement with the manufacturers of these devices.  
10 The first person who would like to speak is Dr. John  
11 Ticehurst, who is an Assistant Professor of Pathology  
12 and Medicine at the Johns Hopkins University School of  
13 Medicine, and the Director of Clinical Laboratories at  
14 the Bayview Medical Center. Dr. Ticehurst.

15 DR. TICEHURST: Good morning, folks, and  
16 I appreciate the opportunity to talk for a few minutes  
17 before you. Would you please refresh my memory, Dr.  
18 Wilson, as to the time that you are allotting me?

19 CHAIRMAN WILSON: About two to five  
20 minutes.

21 DR. TICEHURST: And I apologize that I  
22 don't have a written presentation to give you. I  
23 could provide you with that later. What I would like  
24 to talk to you about briefly today from a somewhat  
25 different perspective than the one that you have heard

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1 so far fall into several categories.

2 When you list several public health  
3 concerns, some of these apply to any assay, regardless  
4 of their classification, and I think you have some  
5 unique opportunities before you for special control.

6 Some particular concerns that pertain to  
7 assays for bioterrorism-associated agents, and  
8 thinking about one of the last questions, and some of  
9 the broader implications of your recommendations  
10 today.

11 I have a model for you for some potential  
12 solutions, and it is full of holes, but it is at least  
13 presented to be provocative, and there are a couple of  
14 bottom lines.

15 I would state that I hope that I am  
16 presenting public health care institutions and level  
17 A labs, particularly those that have been in the  
18 trenches since September of last year.

19 I work in two big hospitals in Baltimore,  
20 Maryland, where we were very much affected by the  
21 anthrax outbreak in the fall. And in putting my  
22 thoughts together today, I talked a bunch with  
23 Patricia Charache, and she used to be a member of this  
24 panel, and who I work with on a daily basis now.

25 To make it very clear, and as many of you

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1 know, I used to work at the FDA, and I am not  
2 representing the FDA today. I do have a perspective  
3 that a lot of people don't have, having worked within  
4 FDA, and would offer that to you.

5 Some of the public health concerns. First  
6 of all, one thing that I always focused on when I  
7 worked at the FDA is what are the implications of  
8 false results or improperly interpreted true results,  
9 okay?

10 And I think in the instance where we were  
11 talking about potential bioterrorist-associated  
12 events, with false positive results, the concern is  
13 when we have a low incidence, perhaps before an  
14 outbreak has been recognized.

15 With a false negative, it is when the  
16 incidence is high, and when people aren't being able  
17 to recognize it. In both cases, there is a big  
18 problem with worried well.

19 In contrast to what some of the other  
20 respondents said -- and this is one reason why I don't  
21 have a written presentation because I was modifying it  
22 this morning -- stand alone use, I think would become  
23 very important in a bio-threat environment.

24 We have been and we are under extreme  
25 pressure in clinical labs at Johns Hopkins to have

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1 assays where we can provide results rapidly to assist  
2 in the diagnosis and management of patients.

3 I think there is another concern that you  
4 need to address, which actually falls into two certain  
5 categories, and those are off-label uses, particularly  
6 if the recommended indication for use would be  
7 epidemiologic.

8 And in the liberal interpretation of  
9 regulations, and having worked inside, I can tell you  
10 that how you classify these things, when people have  
11 different assays to be offered commercially, there  
12 will be extreme pressure within FDA to interpret  
13 things.

14 A new assay may be totally different  
15 within that regulation to enable things to get on the  
16 market more quickly. I think there is a big problem  
17 in this whole arena, particularly by bio-terrorist  
18 agents.

19 The kinds of clinical studies that the FDA  
20 processes normally ask for really can't be done here.  
21 A lot of the controls that one might want really can't  
22 be used in the right environment, and in a typical  
23 environment that they would be used for, even in level  
24 B labs that have been referred to.

25 Another thing that has been borne out is

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1 that what is going to happen in a bioterrorist event  
2 is not going to be what anybody would predict. We  
3 don't know what the natural history is of a  
4 bioterrorist event because the epidemiology is going  
5 to be unique each time when an agent is presented.

6 So you can't really predict it, and  
7 another thing that has been borne out, too, is that  
8 the number or frequency of worried well are going to  
9 outnumber the real patients by a hundred to a  
10 thousand-fold.

11 Some potential solutions. My personal  
12 recommendation is be very wary of Class III and Class  
13 I, and if you want me to elaborate, I will. I think  
14 it is very important to insist on manufacturing  
15 consistency.

16 And although the general controls that Ms.  
17 Shively pointed out called for good manufacturing  
18 processes, they really don't get enforced well unless  
19 they are specified as such.

20 I would recommend a detailed analytical  
21 performance and then once those reagents are being  
22 made available that there is full disclosure of the  
23 limitations, and the types strains and so forth.  
24 Don't hide things. I think everybody has to take the  
25 high road here; government, manufacturers, and users.

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1           The model that we have been developing at  
2           the Hopkins Institutions is to restrict clinical use  
3           by gatekeeping, and this would be something that the  
4           institution would do, perhaps in conjunction with the  
5           FDA.

6           And increasing accuracy by increasing pre-  
7           test probability, and one would allow ordering only in  
8           the context of an expert consultation. For example,  
9           an Infectious Diseases consultation.

10           And, likewise, post-analytically,  
11           interpret the results with the clinicians with an  
12           expert consultant, because we don't know what they  
13           mean clinically, okay? I would also ask the panel to  
14           consider recommending adequate enforceable -- what the  
15           FDA calls post-market surveillance.

16           Traditionally this has not been an area of  
17           strength for laboratory assays, to have post-market  
18           surveillance where there could be data collection and  
19           action, based on what happens after assays get on the  
20           market, no matter who is marketing them.

21           And again, full disclosure, and being very  
22           honest with everybody as much as possible, and what we  
23           know and what do we not know, the bottom lines for  
24           me and for everybody in the room.

25           Ask people to consider the question that

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1 was asked about every assay; would you use it for  
2 somebody who you cared about? And in this context,  
3 would you use it for the public who you care about,  
4 and thank you very much.

5 CHAIRMAN WILSON: Dr. Ticehurst, a  
6 question for you. Would you like to elaborate on why  
7 you would recommend against either Class I or Class  
8 III?

9 DR. TICEHURST: Sure, and again, I am not  
10 representing the FDA, but talking as somebody who has  
11 worked there. For reasons that were never quite clear  
12 to me, the Class III process is extremely cumbersome.

13 And it takes a very long time for the  
14 whole process to go through. It is very well  
15 intended, there have been efforts to streamline, and  
16 I have participated in some of those efforts, but it  
17 is still a very long and lengthy process.

18 I think there is a lot of bureaucracy  
19 built into it, and perhaps in some of the other  
20 processes, particularly things related to good  
21 manufacturing practices. It is very difficult for  
22 companies to gear up for good manufacturing practices,  
23 and the inspections thereof.

24 And maybe even in some of the lower  
25 classifications, maybe they don't go to the same

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1 extent of preparation. Class I, I think my  
2 understanding during the time that I worked at the FDA  
3 was that the current direction was that as many of  
4 these as possible were going to lead towards being  
5 exempted.

6 And where basically it would be up to the  
7 conscience of the manufacturer to adhere to the  
8 general controls that were in place, and in many cases  
9 there would not be submissions to the FDA for these  
10 products.

11 And so it would be a self-regulated  
12 practice in many ways, unless problems occurred.

13 CHAIRMAN WILSON: Okay. Thank you. Does  
14 anyone else have a question for Dr. Ticehurst? Okay.  
15 Thank you. Is there anyone else who would like to  
16 make public comments at this time?

17 DR. TICEHURST: Can I make one more  
18 comment, please?

19 CHAIRMAN WILSON: Go ahead.

20 DR. TICEHURST: I'm sorry, but I forgot to  
21 mention this in context. I take issue with some of  
22 the comments that were made about Level A labs before  
23 and I sort of said this to some extent.

24 I think at least within Maryland the  
25 public health labs were overwhelmed during the fall,

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1 and again I mentioned the point that there was a lot  
2 of pressure on those of us in what might be called  
3 level A labs, many of which have lots of expertise for  
4 doing the kinds of things.

5 I think a good thing to do would be to --  
6 and I will just mention that this is not your purview,  
7 but that the public health network be reexamined to  
8 see where it can be expanded when necessary, because  
9 from my point of view, the public health labs had a  
10 lot of difficulty keeping up, and we in the level A  
11 labs really had to be prepared and need to be prepared  
12 to do a lot more organism-specific diagnosis on our  
13 own up through biosafety level three. Thank you.

14 CHAIRMAN WILSON: All right. If there are  
15 no other -- yes, Dr. Reller.

16 DR. RELLER: Dr. Ticehurst, I  
17 intentionally wanted to be provocative about the level  
18 A laboratories. What about another paradigm?  
19 Recognizing the pressures -- there is a balance here,  
20 and one of the reasons that public health laboratories  
21 are overwhelmed is because they have been under-  
22 supported.

23 So if we have an atrophied public health  
24 laboratory system, then one could use the argument  
25 that we need level A because we don't have level B.

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1 As part of a national response, what about the  
2 possibility of strengthening the B, and enlarging the  
3 vision?

4 For example, in North Carolina, selected  
5 laboratories throughout the state were actually asked,  
6 and we volunteered technologists to work in the state  
7 laboratory to help them through the crunch.

8 The state laboratory relies on selected  
9 level A laboratories for consultation, advice, and it  
10 is sort of like deputizing a level A laboratory.  
11 Could that not be incorporated into actually  
12 strengthening the public health network by having  
13 laboratories that are of recognized expertise,  
14 proficiency, et cetera.

15 Where I have problems with level A, and  
16 with Dr. Ezzell's comment that we need to get gamma  
17 phage, or implied, that we need to get gamma phage so  
18 that a laboratory who is uncertain could get through  
19 the dilemma.

20 And I think there are laboratories where  
21 this could lead to problems. And particularly when  
22 tests, any tests, are applied in the absence of the  
23 clinical context, and consultation that you emphasized  
24 was an important part of your effectiveness.

25 So in considering how we classify these

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1 things, it seems to me that we should also think about  
2 not -- the world as it necessarily has been, but the  
3 world that could be and maybe should be. Comments in  
4 relationship to that, and you urging the level A  
5 laboratories have these reagents available?

6 DR. TICEHURST: Well, first of all, I am  
7 surprised to hear that you are being provocative. I  
8 have never heard that before. Second -- and it is not  
9 my nature either as you know -- but secondly, I think  
10 there was a question there about whether one might,  
11 instead of -- and I was sort of emphasizing direction  
12 of resources or considering the use of these types of  
13 assays in a level A lab.

14 And I think that your question was, well,  
15 why not expand level B capabilities either directly or  
16 indirectly through deputies or deputizing. And I  
17 think that is a fine concept, and I think one of the  
18 things in any of these scenarios that everybody has  
19 got to be really flexible.

20 And I think that people have to think, and  
21 when I say people, I mean everybody from FDA,  
22 manufacturers, CDC, you name it, they have got to  
23 think public health and put everybody's interests at  
24 stake here.

25 I think one of the problems and that one

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1 of the directions that we have been working on in the  
2 Hopkins' institutions is a sort of qualitatively or a  
3 qualitative concern.

4 The question about expanding the level B  
5 capability, no matter how you do it, is it simply  
6 quantitative? In other words, are there enough tests  
7 and people to handle the workload, or is it also  
8 qualitative, in terms of the technology.

9 The discussion before I eventually got  
10 around to talking about PCR techniques and so forth.  
11 I think that -- and again I agree -- I think that the  
12 public health labs in this country have been neglected  
13 to a large extent for a long period of time.

14 If you are going to expand them either  
15 directly or indirectly, you are going to need to make  
16 sure that you do it technologically, qualitatively, as  
17 well as quantitatively, and that is not something that  
18 you can make happen overnight.

19 Where you have the advantage now, at least  
20 in certain level A labs, many academic medical centers  
21 today have a lot of expertise in modern technology  
22 like PCR, where it would be relatively easy for them,  
23 whether deputized or whether level A privileged, or  
24 whatever you want to call it, would be able to either  
25 supplement the public health system, or at least be

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1 able to provide for their institution's patients.  
2 Does that answer your question?

3 DR. RELER: Well, I appreciate your  
4 perspective, and I think it would be -- it is not only  
5 the number of people. I mean, I agree with you that  
6 the cutting edge technology, I believe, needs to be in  
7 the public health sector, as well as the academic  
8 centers.

9 I think when we talk about technology,  
10 there is also another aspect that is important, is  
11 that sometimes the technology in my view, the cutting  
12 edge technology and academic medical centers may be --  
13 the technological possibilities may outstrip the  
14 clinical and perhaps public health capacity to  
15 appropriately apply that technology.

16 CHAIRMAN WILSON: Dr. Thrupp.

17 DR. THRUPP: Your suggestion is perhaps a  
18 reclassification of laboratories, and you need an A-1  
19 and an A-2 category, not to increase the bureaucracy.  
20 But I was going to come back to your experience.

21 You mentioned the Maryland public health  
22 facilities were overwhelmed, and so it is a lot easier  
23 in hindsight obviously, but has anybody taken a look  
24 in retrospect at the overwhelming issues that came up  
25 in October.

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1           And from the standpoint that we have all  
2           have mentioned, or that everyone is wanting to have  
3           available, namely a good level one standard procedure  
4           approach, together with clinical and epidemiological  
5           consultations at the local level with infectious  
6           disease, or if the health department is overwhelmed,  
7           at least have the local hospital have their team  
8           evaluate the episode or the suspicious episode, or  
9           whatever.

10           In retrospect, how many of this  
11           overwhelming workload for the public health labs could  
12           have been adequately handled at the level A level,  
13           with appropriate consultation and standard  
14           microbiology procedures?

15           DR. TICEHURST: I think that the way that  
16           scenario evolved, and as I participated in it, and  
17           from what I saw on the side, was that it was a first  
18           episode, and no matter what happened, and no matter  
19           who absorbed the workload, they were going to be  
20           overwhelmed.

21           There was a lot of flying by the seat of  
22           the pants, and that is not a criticism. That was a  
23           reality. It goes back to my point about the natural  
24           or there is no natural history, and you can put  
25           natural in quotes.

1           The way things have evolved was not the  
2 way that anybody predicted. And that makes it very  
3 difficult to -- and again as I said, to try to be  
4 predictable as to how to deal with things, but I do  
5 think that a lot of lessons were learned about the  
6 kinds of things that need to be in place.

7           We now have experience with a bioterrorism  
8 event, that in terms of total cases, which are tragic  
9 of course, are very small. But the overall impact was  
10 huge, and again because of this huge number of worried  
11 well or potentially exposed, and so forth.

12           And I think there are people that are  
13 reexamining -- well, I can't speak to what the  
14 Maryland state public health labs have done, or might  
15 be doing to reexamine.

16           I think that if the -- that on the  
17 idealistic side, if the kinds of consultations and so  
18 forth we were just talking about took place, yes, a  
19 number of the influx of specimens and so forth would  
20 be much smaller.

21           But then you get to the -- well, what is  
22 the reality, and that is where some of the holes come  
23 in. How many consultants are there to go around to  
24 make that recommendation.

25           Are you going to extend it down to

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1 fellows, as well as attendings. You know, you reach  
2 a point where that system gets overwhelmed, and I  
3 think that we can learn lessons, but I think that this  
4 is part from my perspective one of the problems before  
5 you today, which is that you are being asked to make  
6 recommendations on things where you can't really --  
7 you can't even necessarily recommend what ought to be  
8 done.

9 And that's because the scenario, at least  
10 when we are talking about bioterrorism, can't be  
11 predicted. But on the other hand, there is obvious  
12 perceptible public health benefit to these things that  
13 are plausible.

14 And if you do the traditional long list of  
15 things, or even the short list of things that the FDA  
16 would traditionally require, these things can be kept  
17 off the market, and add public health plausibility,  
18 and I think that is doing just as much harm.

19 CHAIRMAN WILSON: Okay. Mr. Reynolds.

20 MR. REYNOLDS: A real quick question. As  
21 someone in a public health laboratory that was  
22 involved in this, I know that in our state lab, the  
23 number of clinical isolates that were referred to us  
24 because they were suspicious were actually fairly  
25 small, maybe a couple of dozen.

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1                   So that was not a problem. But we were  
2 indeed inundated because of the environmental samples,  
3 and I don't think that anyone is recommending that  
4 level A laboratories work with environmental samples.

5                   DR. TICEHURST: I think the answer to that  
6 is right, although I have heard of scenarios where  
7 level A laboratories received environmental specimens  
8 and ran into big problems because of that.

9                   I don't know about the total number of  
10 specimens, and what the safe level was. Some of the  
11 overwhelmed pertained less to isolates than to  
12 antibody detection, potential for exposure.

13                   There was also the question that came up,  
14 which I think is relevant to the discussion today, is  
15 naris sampling, which really is an environmental  
16 sample when you get down to it.

17                   But that caught the attention of  
18 everybody, and that is what public, clinicians,  
19 everybody wanted to sample everybody's noses, and I  
20 think that perhaps falls into the purview of the  
21 discussion today.

22                   CHAIRMAN WILSON: Dr. Gutman, would  
23 testing for things that are in an epidemiologic  
24 environmental type of testing, does that fall under  
25 the purview of the FDA?

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1 DR. GUTMAN: I feel it is purely  
2 epidemiology that would fall outside of the purview.  
3 I might differ with Dr. Ticehurst about nasal turgor  
4 [phonetic], but if it was clearly environmental stuff  
5 on letters, or post boxes, that clearly is  
6 environmental, and that also falls outside.

7 CHAIRMAN WILSON: Okay. Thank you, and  
8 thank you, Dr. Ticehurst. I would like to end at this  
9 point to close the open public hearing, and at this  
10 point, I think we will go ahead and take our lunch  
11 break now.

12 We were scheduled to do an open committee  
13 discussion on either side of the lunch hour, and I  
14 think it would be easier at this point just to start  
15 that right after lunch.

16 And I would like everybody to come back  
17 promptly at one o'clock, if possible. Thank you.

18 (Whereupon, at 12:00 p.m., a luncheon  
19 recess was taken.)

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

21 (1:13 p.m.)

22 CHAIRMAN WILSON: I would like to begin  
23 the open meeting discussion. I would like to comment  
24 that this meeting is open to public observers. The  
25 public observers may not participate without the

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1 specific request of the chair person.

2 For about the next -- we are going to  
3 allocate about another hour or so to have a committee  
4 discussion prior to making a final recommendation and  
5 vote.

6 At this point, I would just like to open  
7 up the discussion to members of the committee, and  
8 again, I would remind everyone to please speak into  
9 the microphone, and if you would like someone either  
10 from the audience or the FDA to participate, please  
11 indicate so.

12 Would anyone like to begin the discussion,  
13 or does anyone have a question that they didn't get  
14 answered this morning? Dr. Smith.

15 DR. SMITH: Well, I guess I was part of  
16 sort of what happened in Washington, D.C., and seeing  
17 people come to our hospital for screening. And I  
18 think there was so much chaos at the time, that as I  
19 was trying to sort this out in my mind, I realized  
20 that our mission is one of trying to classify this,  
21 but at the same time I can't discount how I know how  
22 this test is actually going to be used, and in some of  
23 the discussion that we have had around the table, I  
24 think.

25 I personally would like to see the logic

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1 particularly available, but at the same time we have  
2 to put it out there with controls and specific  
3 clarifications for clinical guidance.

4 I think that without that sort of  
5 information going out to the communities, except to  
6 the A level labs, and which most of the hospitals in  
7 Washington, D.C. are, and trying to use this test in  
8 a way to help the community at large and not to panic.

9 And that is how I see this particular  
10 device being used in a lot of ways, and not just for  
11 the individual person's culture result. But at the  
12 same time trying to help a community who was in panic.

13 And I leave that out for sort of everyone  
14 to think about, and trying to decide on how we should  
15 classify this, and what kind of restrictions may or  
16 may not be put on the device, but I do think it should  
17 be available for level A labs.

18 CHAIRMAN WILSON: Mr. Reynolds.

19 MR. REYNOLDS: My comment along those  
20 lines is that I don't have a major problem with that,  
21 but I think that you need to separate your populations  
22 into two distinct populations. One would be the  
23 screening populations, which probably should not get  
24 tested anyway, but since we can't get around that,  
25 they are going to get tested.

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1           And other than the people that have actual  
2 real clinical presentations. I mean, if somebody  
3 comes in and says that there is a suspicion to  
4 cutaneous anthrax, and you isolate an organism from a  
5 blood culture or wound culture, and I think regardless  
6 of what you get in that level A laboratory, that  
7 should go up the line.

8           And that that should be part of the  
9 recommendation built into that, and that would be  
10 subjected to further testing so that it would get a  
11 PCR and it would get a full battery of testing,  
12 because even if the phage is a good test, we know that  
13 in the literature that there are reports of both false  
14 positives and false negatives.

15           So that would be my only recommendation,  
16 that you basically have these two different groups,  
17 and the screening group, I don't have any problem with  
18 you do with them. But anyone who actually has an  
19 actual clinical presentation, any isolates that  
20 should go up the line.

21           CHAIRMAN WILSON: Dr. Ng.

22           DR. NG: I am in a high complexity level  
23 A lab. Yet, I don't do any stage testing. So I am  
24 very concerned that if that should be made available  
25 would we be able to maintain competency and

1 proficiency in the rare case where it would be needed.

2 I am also struck by the relative lack of  
3 information on how these tests are performed as  
4 alluded by Drs. Brown and Ezzell. But in the  
5 background information that we have been provided, in  
6 1951 the studies showed that 2 of 56 other B.  
7 anthracis strains reacted positively in the gamma  
8 lysis.

9 We see 8 of 70 in a different study, a  
10 1958 study, and 8 of 70 B series serum mycocides, also  
11 light.

12 And we see in a 1963 study that only 63 of  
13 74 B. anthracis strains, et cetera, et cetera. So  
14 there is this definite false negative, as well as  
15 false positive, rate. And I don't feel that I have  
16 enough information to decide is it a good enough test  
17 to put in the hands of the relatively inexperienced  
18 a.k.a. level A lab.

19 I would also like some background  
20 information, and if you are using the test in  
21 conjunction with the gamalysis and appearance of the  
22 colony, the non-hemolysis, the non-motility, and the  
23 gamma phage life, and what are the relative false  
24 positives and false negatives of each of those tests.

25 And then all together so that we can sense

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1 what are the risks of false positives and false  
2 negatives.

3 CHAIRMAN WILSON: Dr. Ezzell.

4 DR. EZZELL: Once again, we didn't bring  
5 data, our data, to show you today. The interpretation  
6 of some of these earlier studies had to do with the  
7 way that people were interpreting whether or not it  
8 was positive or not.

9 In some of the cultures, where you had a  
10 continuous line of the culture, and you added the  
11 phage, some laboratories, some laboratories were  
12 scoring that if you had any kind of indentation, even  
13 though it did not cause lysis or cause a plaque  
14 formation, that this was considered a positive.

15 So some of these laboratories had  
16 variations in how they were interpreting the assay.  
17 And in our hands we have noted a very small number of  
18 some other bacillus, B. anthracis series, what will  
19 give us a positive.

20 But we have found very few. We have  
21 looked at well over a hundred strains of B. anthracis,  
22 and these have -- one thing that we have noted, and  
23 this has a bearing on how the application of this  
24 assay, which has made a big difference in the  
25 performance of it, is that we have established, and we

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1 have gone through the validation of this, to show that  
2 you need to look at the phage in two different  
3 concentrations of inoculum, and so we go to a two  
4 quadra streak.

5 And this is one thing that we have found  
6 that has improved the performance of this assay, and  
7 this was still a limited study that we did, but we  
8 still looked at quite a broad range of isolates.

9 So I think there are going to be some  
10 performance characteristics that are going to be  
11 different or are going to differ from these earlier  
12 studies because of some things that we have found  
13 since then.

14 But this assay, I do not think, should  
15 ever be used by itself as a stand alone assay, and I  
16 think that especially in those cases of *B. cereus*,  
17 where these strains are hemolytic, as opposed to the  
18 *B. anthrax*, which is not.

19 I think that when we take non-hemolysis --  
20 and gamma phage, this assay is going to be -- I think  
21 it will have a much better performance than some of  
22 these earlier reports had indicated.

23 And also based on the fact that we had  
24 going to phage on this particular strain, we have had  
25 pretty good results with it. But I can say that this

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1 assay is not meant to be a stand alone assay.

2 CHAIRMAN WILSON: Dr. Ezzell, are these  
3 assays evenly -- I mean, given that some of these  
4 reports go back 30 to 35 years, are these even really  
5 the same assays that were originally described and  
6 tested?

7 DR. EZZELL: That is an interesting  
8 question. We do not have any of those phage from  
9 those earlier studies. All we have is the gamma phage  
10 that was originally supplied to us by CDC many years  
11 ago by Lou Cherry, and that we have propagated and  
12 tested on various other and different strains to  
13 produce a phage.

14 The phage as we produced it appears to  
15 work very well in our hands, but as I said, one thing  
16 that we have discovered is that there are variations  
17 from strain to strain of the B. anthracis, and that is  
18 a potential problem.

19 But like I said, we have found that by  
20 going to a two quadrant streak, and doing two  
21 different concentrations, that this has cleared up  
22 some of the iffy results that have been noted earlier.

23 CHAIRMAN WILSON: Dr. Ng.

24 DR. NG: In just hearing your discussions,  
25 in fact these details and subjectivity of the

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1 interpretation, as well as the new variations in the  
2 assay, make me say that I want to leave this with my  
3 State lab, and you are not dealing with the unique  
4 issue with the clinicals, and so now it is an iffy and  
5 leave it to the experts.

6 DR. EZZELL: This assay, like a lot of  
7 assays, should never be put in the hands of people  
8 that are not properly trained, and have actual  
9 experience, and also should always be run with proper  
10 controls.

11 And to go back to some of the earlier  
12 comments about having these assays show up and be  
13 handled by inexperienced personnel, that should never  
14 happen. And actually the duty of the level B  
15 laboratories, and who are directly above those level  
16 A laboratories, if this assay were to be put in level  
17 A hands, that these people should be trained by the  
18 level B lab right above them should be responsible for  
19 making sure that they are properly trained.

20 CHAIRMAN WILSON: Dr. Nachamkin.

21 DR. NACHAMKIN: So we are allowed to  
22 consider each of these class of reagents separately,  
23 and we don't have to consider them as either all  
24 none? So, for example, we could say the gamma phase  
25 should be a Class II type of device, and the antigens

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1 that are produced for doing serologic surveys are  
2 Class I, is that correct?

3 DR. EZZELL: That's right.

4 DR. NACHAMKIN: And we have not really  
5 discussed very much about the antigens, and in my  
6 mind, antigen production and the assays for measuring  
7 the antibodies with surveys really have fairly little  
8 implication, in terms of diagnostic laboratories.

9 So I am not too concerned about that, but  
10 it is clear from the discussion that the gamma phage  
11 is not a simple test to do. That there are lots of  
12 variables that go into doing the test, and it is  
13 likely that laboratories are going to need to have a  
14 reagent like this at some point in the future for a  
15 variety of reasons.

16 One is that we can't count on the public  
17 health infrastructure to be funded to support this.  
18 I mean, if the government does what they normally do,  
19 is that they put a lot of money in now, and then they  
20 will yank it a few years from now when it is  
21 politically not sensitive.

22 And so I am concerned about the long-term  
23 viability, in terms of the public health ability to  
24 support continued outbreaks or BT events. And then  
25 there are issues about getting strains from the local

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1 labs to the public health labs for testing.

2 We have heard a lot about UPS instituting  
3 a gamma radiating or ionizing the radiators for all  
4 their boxes. There are no regulations now to examine  
5 certain products. So anything that I might send via  
6 a courier could get irradiated before it gets to the  
7 State laboratory.

8 The mechanisms for transporting them from  
9 hospitals to State laboratories are not well worked  
10 out. We have experienced some problems ourselves in  
11 Philadelphia in October, with just trying to get  
12 something couriered from the City lab to the State  
13 laboratory, which took two days.

14 If we had a reagent available, we would  
15 have had the answer right then. So in the event of  
16 any of these scenarios, I don't think everything is  
17 going to work perfectly.

18 So we just have to take that into account  
19 when classifying these devices as to where it might it  
20 be used in the future, and not necessarily what the  
21 current policy is, and whether the policy is correct  
22 or not. I mean, we can't decide the policies here.

23 CHAIRMAN WILSON: Good point. Dr.  
24 Zabransky.

25 DR. ZABRANSKY: I have a number of things

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1 that are related and unrelated. First of all, putting  
2 in Class II versus Class I, and I will just say Class  
3 III in my mind is out of the question.

4 But putting it in I or II is not going to  
5 dictate where the test is going to be done. To me  
6 that has to be done or controlled by the -- what has  
7 been described as the special controls, which we could  
8 put into Class I by who you distribute the test to.

9 The other aspect of this, and again I am  
10 thinking of the phase testing in particular, the  
11 aspect of quality control of this particular test. I  
12 don't know, and I am going to ask Dr. Gutman if he can  
13 comment on this, but can we define in the special  
14 controls under the labeling how those controls for the  
15 tests can be done if we put the test into Class I. Do  
16 you follow me?

17 DR. GUTMAN: Let me make a correction  
18 first. Actually, the special controls would require  
19 you to classify this as Class II, and if you decided  
20 that it would be Class I, then you would have that  
21 considered as quality control.

22 DR. ZABRANSKY: Oh, excuse me.

23 DR. GUTMAN: I am actually not sure. Can  
24 quality control be considered or be part of a special  
25 control for Class II?

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1 (Brief Pause.)

2 DR. GUTMAN: Yes. The answer is yes.

3 DR. ZABRANSKY: Well, based upon that,  
4 with the special controls that can be set up as far as  
5 distribution, which would be to only certain types of  
6 labs, either by virtue of their level, which might be  
7 assigned by CDC regs, which would be the B level, or  
8 perhaps with certain education and training, which  
9 would be the larger labs, university labs.

10 And then with the adequate description in  
11 the labeling as to how the tests are to be done, if  
12 would seem to me that it could be put into that kind  
13 of a category.

14 The problem is how fast can the  
15 regulations or the new rules be written to address  
16 that, as opposed to putting it into Class I  
17 completely, which would allow it to be quickly  
18 marketed so to speak. And I see a comment coming up  
19 here.

20 DR. EZZELL: Well, actually at least at  
21 this point in time, the difference between Class I and  
22 Class II, in terms of a non-exempt product, this would  
23 be reserved products as Class I and a Class II  
24 product, unless you chose to exempt this Class I.

25 But for a reserve product the review

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1 process is not terribly different. Special controls  
2 do kick in, but the bottom line is that we still want  
3 to see performance, and actually the heart of the  
4 challenge here is the challenge that Dr. Ticehurst  
5 brought to the table, which is that it will be hard to  
6 deal with this because you won't see the normal  
7 clinical data sets that we have come to know and love.

8 I want to correct what I said. Quality  
9 control could be applied as a special control if you  
10 were to make this a Class II, and your ability to put  
11 recommendations on the table either to have special  
12 labeling, restricted labeling, that labeling could be  
13 for the product itself.

14 That labeling could spill over into the  
15 test report if you thought it was appropriate; and/or  
16 your ability to define some kind of use, high  
17 complexity lab, or low complexity lab, public health  
18 response lab, or whatever you decide to put on the  
19 table.

20 The restrictions in use and labeling  
21 actually can be associated with Class I, and we have  
22 actually a couple of examples of Class I products that  
23 are actually exempt, but restricted in the way that  
24 they are distributed.

25 So you have a reasonable amount of freedom

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1 to put special controls on and then put restrictions  
2 on as well, depending on what the comfort level is.

3 DR. ZABRANSKY: Do you want to address  
4 what I was talking about, because I do have something  
5 else.

6 DR. EZZELL: I totally agree with your  
7 comment about the -- this discussion, it was my  
8 impression that it would deal primarily with the task  
9 and not with which laboratories are going to be using  
10 the test.

11 Early on it was brought up where did I see  
12 that possibly being used, and I just happened to  
13 mention level A laboratories. But perhaps that still  
14 needs to be resolved within the CDC and the LRN and  
15 try to resolve those issues about how far those tests  
16 would be taken.

17 I would just make the observation that  
18 perhaps some Level A labs may have benefitted from  
19 some other test they could use to give some sort of  
20 added degree of assurance that they were not dealing  
21 with B. anthracis.

22 But once again I think this issue about  
23 whether or not it is going to be a Level A laboratory  
24 or not is something that should be perhaps -- well, my  
25 suggestion would be that it should be something that

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1 should be resolved within the CDC and LRN  
2 infrastructure to determine how that assay would be  
3 managed, and I think that this would be something that  
4 would be desirable.

5 And so I was just going back to one of  
6 your earlier comments about the distribution of this  
7 assay.

8 DR. ZABRANSKY: Our next comment had to do  
9 with the differentiating of the three tests that we  
10 are looking at. Dr. Ng mentioned that she couldn't do  
11 the phage testing, and I don't know how many labs do  
12 phage testing any more.

13 I can think of only possibly two, CDC, and  
14 maybe the Michigan State labs, and possibly some  
15 others. I used to do phage testing, but I don't think  
16 I could start it up again in a lab if I wanted to do  
17 it today.

18 But on the other hand, most laboratories  
19 do do fluorescein antibody testing, hospital  
20 laboratories, and so this is the type of thing where  
21 that sort of a test might be suitable to be put into  
22 a level A lab.

23 And as far as the antigen test is  
24 concerned, I don't know where I would want to put that  
25 right now.

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1 CHAIRMAN WILSON: Dr. Thrupp.

2 DR. THRUPP: I was going to throw out a  
3 similar question. There have been a number of  
4 comments about the phage, but of course an antibody is  
5 done in the level A lab, and is more amenable to what  
6 people are used to doing, in terms of controls.

7 And so I wondered if you could comment a  
8 little bit further on your experience with FA,  
9 because, for example, on the CDC and in the summaries  
10 that were produced, there are some comments which I  
11 didn't find it in the papers, but for example, that  
12 the capsules are only produced on certain media, and  
13 that they can be lost on subculture, and if they are  
14 going to be lost readily so that false negatives could  
15 be a real problem, or if the media on which capsules  
16 are produced is going to be difficult to produce, and  
17 produced on standard media, there is some other  
18 questions that would be relevant, in terms of whether  
19 we are -- and grant that nobody is preparing to  
20 present a proposal with data, but just a feeling for  
21 whether the FA test is really a slam dunk, or has it  
22 got lots of holes in it that would present control  
23 problems.

24 DR. EZZELL: There are a number of  
25 problems that can occur, especially with the capsule

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1        assay, and that the organism, when it is derived  
2        directly from the clinical sample -- blood or a tissue  
3        -- that that organism is invariably going to be  
4        decapsulated.

5                    And typically you can see that capsule  
6        with other capsule stains, or you can see somethings  
7        in a regular gram stain, you can see the halo around  
8        the bacillus.

9                    To do a stain on that original material,  
10       there is a lot of capsule that is surrounded with some  
11       high tices and background problems, and sometimes if  
12       the assay is not performed correctly, and you are  
13       doing it directly on a clinical sample, and the  
14       capsule is constantly sloughed off and there is some  
15       background.

16                   But still the stain, you can see the  
17       capsule fluoresced very nicely. The problems that we  
18       have run into when you come off a culture is typically  
19       that the capsule requires elevated CO2, and typically  
20       we go through and get capsule production when you grow  
21       it on a mutually auger, with .8 percent bicarbonate,  
22       and you incubate in the presence of 5 percent CO2.

23                   So a laboratory that is going to do that  
24       directly off a culture has to go back and make sure  
25       that the organism is incubated either in a broth with

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1 .8 percent bicarbonate, or in an auger, an auger  
2 culture that has .8 percent of bicarbonate, along with  
3 some CO2.

4 When you do this, under standard methods  
5 where you dry the organism down on to a slide, and  
6 then come back and fix it, and then do your assay, the  
7 problem with that is that quite often these bacilli  
8 will slough off, because that capsule is loose enough  
9 that when you try to wash, you end up with ghost  
10 images of where the capsule was still stuck to the  
11 slide.

12 That is a problem, and that is one reason  
13 that there is some -- that when we worked with CDC on  
14 some of the methodology, because at USAMRIID you have  
15 to look at these FAs actually under wet mount and not  
16 poured on top of the slide.

17 But there is a problem when you try to do  
18 standard methods, and so in that regard there is a  
19 problem with that particular assay, unless you use  
20 special methods, and the problem that you will run  
21 into is that typically people do not look at their  
22 assays under wet mount in most Level A labs.

23 So these are problem areas that have yet  
24 to be resolved with regard to that.

25 DR. THRUPP: But your comment was well put

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1           though at the beginning, that if you are dealing with  
2           suspicious clinical circumstances, and you have a  
3           blood culture, or tissue, that is really suspicious,  
4           that is the physiologic circumstance where the direct  
5           would be positive, because there would only be a  
6           capsule there.

7                     DR. EZZELL: Yes, absolutely.

8                     DR. THRUPP: So that might be worth  
9           considering. Is ormine or a counter-stain necessary,  
10          especially when you are dealing with tissue with that?

11                    DR. EZZELL: What we have found in tissue  
12          is that it depends on the age of the tissue, and how  
13          readily it was fixed. That we see some variations in  
14          how far the capsule has begun to slough off the sills,  
15          and how much background we will see.

16                    But we have had great success in picking  
17          up encapsulated bacilli out of tissues, and also we do  
18          a dry down blood smear, but even then I can say that  
19          you are going to run into some problems.

20                    It is a little bit of a background problem  
21          because the capsule has sloughed off.

22                    DR. THRUPP: But without a counter-stain  
23          and doing it direct?

24                    DR. EZZELL: Just doing a direct gram  
25          stain, you can see halos typically running with

1 bacilli. I hope that I have answered your question  
2 right.

3 CHAIRMAN WILSON: Okay. Other questions  
4 or comments at this time? Dr. Ng.

5 DR. NG: I want to respond to my  
6 colleagues. You are right that a direct FA is a  
7 second line test and it certainly is what we do for  
8 legionella and other bugs like that.

9 But when I hear about this, I get even  
10 more nervous about it, and I think what we are all  
11 suffering about is the true lack of how this performs,  
12 and I recognize that you probably don't have an update  
13 to tell us how it performs.

14 But just kind of an understanding of how  
15 we would interpret that result, and the likelihood  
16 ratio of a positive test, meaning it is really an  
17 organism, or a negative, meaning you have really ruled  
18 it out.

19 And nothing that I have heard here says  
20 that any of those tests are a hundred percent or  
21 diagnostic in trained hands, let alone in high  
22 complexity labs, where we would do this test once  
23 every year, or once every years, and maintaining  
24 competency and proficiency would be an issue.

25 DR. THRUPP: Well, Dr. Ng, the latter

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1 point is well taken. It is going to be rare that it  
2 happens. On the other hand, if you have got a  
3 clinically suspicious circumstance in a septic  
4 patient, and you have got positive blood, and the  
5 anthracis grows rapidly, and you see gram positive  
6 bacilli in that blood.

7 And within a matter of hours, you could  
8 have an FA confirmation; whereas, if you are going to  
9 wait for hemolysis, and subculturing, and phaging, or  
10 even PCR later, then there is a rapid assay out there  
11 that would from what we are hearing would actually  
12 work.

13 Now, whether it is practical is another issue.

14 CHAIRMAN WILSON: Dr. Ng.

15 DR. NG: Well, I want to think about the  
16 acute patient issue, versus the epidemiology here, and  
17 so in that situation, if you tell the ID guys that you  
18 have got a gram positive tissue growing like busters  
19 in blood culture, I would hope that they would have  
20 covered that possibility so that the identification of  
21 the organism, and the treatment is not dependent on  
22 the delay that it will take to ID the organism.

23 DR. THRUPP: Well, some of the sirius grow  
24 pretty rapidly, too. Now, not as rapidly I don't  
25 think, but there could be --

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1 DR. TUAZON: But the scenarios are very  
2 different for the yersinia pestis and --

3 CHAIRMAN WILSON: Mr. Reynolds.

4 MR. REYNOLDS: One of the concerns that we  
5 have talked about at our laboratory, insofar as making  
6 these tests more widely available, is in order to  
7 actively and safely do the test, at a minimum you are  
8 going to have to maintain the A-virulent control  
9 strain.

10 Short of doing PCR, the A-virulent control  
11 strain is indistinguishable from virulent disease  
12 causing strain, and one of our concerns is how widely  
13 do you want that A-virulent control strain  
14 disseminated among the public.

15 But from a BT point of view, or point of  
16 view of it being used, you would have to do the same  
17 amount of workup to verify the A-virulent control  
18 strain is the actual virulent strain that actually be  
19 the -- and so we are just concerned about it getting  
20 into the wrong hands if it is too widely disseminated.

21 So when you start talking about some of  
22 these Level-A laboratories where you don't have a high  
23 degree of security, and things of that nature, then it  
24 becomes a concern to us.

25 DR. NG: I just want to make a comment to

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1 Dr. Thrupp. Well, we are here and we are discussing  
2 history, right? Because we firmly believe that the  
3 test in the future will be hopefully a nucleic acid  
4 based test.

5 We are dealing with a blood culture bottle  
6 at 10 to the 9th, or 10 to the 12th organisms per mil.  
7 Excuse me, but I don't see why you need to amplify  
8 that. That ought to be a direct hibernation assay  
9 that ought to be fairly quick.

10 So in that situation, an assay, a direct  
11 hibernation, it doesn't matter. You probably will  
12 have a tool that can be better controlled at the level  
13 of a level A lab to make the rapid diagnosis.

14 DR. EZZELL: I think we were restricted  
15 here to things that were prior to 1976, but yes, we  
16 have modern tools available now. And one more comment  
17 about the bacilli in the blood. I will throw the  
18 question out to you.

19 I know of no other bacillus that will form  
20 a capsule like this in blood. Do any of you know  
21 one?

22 DR. NG: Megaterium.

23 DR. EZZELL: Megaterium forms a capsule in  
24 blood?

25 DR. NG: That is what the paper says.

1 DR. EZZELL: Right, but as far as -- okay.  
2 But anyways the B. anthracis is one of the  
3 characteristics, that it forms a very nice capsule  
4 around the terrain. But also based on the size, the  
5 bacillus could be much smaller.

6 CHAIRMAN WILSON: Okay. Could we have the  
7 FDA put the questions up on the screen for everyone to  
8 see, please.

9 (Brief Pause.)

10 CHAIRMAN WILSON: Okay. The questions  
11 that the FDA have asked us to consider are shown on  
12 the screen. The first question is are you aware of  
13 any other known risks to health presented by the use  
14 of the types of devices identified by FDA as  
15 preamendments reagents for the identification of  
16 bacillus anthracis?

17 The second question is are you aware of  
18 any additional information, not by presented by the  
19 FDA, which would affect safety and effectiveness of  
20 this type of device?

21 I think from the discussion this morning  
22 and this afternoon that the main concern in terms of  
23 safety seem to center around the issue of what you did  
24 with the clinical results, and how the tests are  
25 interpreted.

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1 I have not heard a lot of discussion about  
2 the other aspects of safety; that is, actually using  
3 these assays. I think Dr. Ezzell and others have  
4 commented that you can do this pretty safely, even at  
5 bio-safety level two conditions.

6 So I think the real issue here that we are  
7 all trying to grapple with is what do you do with  
8 these results.

9 The third question that has been asked is  
10 what level of controls are sufficient to provide a  
11 reasonable assurance of safety, and the fact that  
12 these types of devices; that is, general controls,  
13 general and specific controls; and premarket approval.

14 And then the fourth question is do you  
15 believe that restrictions on sale, distribution, or  
16 use are necessary to provide reasonable assurance of  
17 safety and effectiveness for these types of devices.

18 And then, Ms. Shively, if you could put up  
19 the form. And so for those of you who have not seen  
20 this form before, in some sense this is simply a  
21 rewording of the questions that have just been shown  
22 up there.

23 And what we have been asked to do is to  
24 vote on these sequentially, because that is the way  
25 that the form is designed. And so at this point I

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1 would like to begin that process, beginning with the  
2 very first question.

3 I don't think that members of the audience  
4 can probably see it, and so I will read it to you. In  
5 Question Number 1 on this form, it states that if the  
6 in vitro diagnostic product, or information derived  
7 from its use, potentially is hazardous to life,  
8 health, or well-being when put to its intended use.

9 So this is the first issue that we have  
10 been asked to vote upon. Unlike for those of you who  
11 have been to previous panel meetings, this is not a  
12 condition where we will vote either for approval, non-  
13 approval, or approval with conditions.

14 This is just a straight up and down yes or  
15 no vote on each of these questions so that we can  
16 complete this sequentially as we go through the form.  
17 And as we go through, rather than doing the usual vote  
18 of individuals, I will probably just ask for a show of  
19 hands from the panel members. Dr. Gutman.

20 DR. GUTMAN: Yes, we just need you or the  
21 committee to clarify whether you are going to address  
22 these sequentially as three separate items, or whether  
23 you are going to bundle them and treat them as a  
24 single item.

25 CHAIRMAN WILSON: I think from what I have

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1 heard from the panel members that everyone would like  
2 to do these separately for the three different  
3 products. Yes?

4 MS. SCHULMAN: Marjorie Schulman, FDA.  
5 Then we will have to fill out the form three separate  
6 times to vote on the device?

7 CHAIRMAN WILSON: That's fine. All right.  
8 Dr. Ng.

9 DR. NG: I'm sorry, and I know that we  
10 discussed these in two different categories, but I am  
11 actually in favor of bundling them all together.

12 CHAIRMAN WILSON: Okay. Then we will have  
13 to take a vote on that then. I will take that as a  
14 motion then, Dr. Ng, that you would like to have them  
15 voted on as a bundle. Does anyone want to second that  
16 motion? Dr. Reller.

17 DR. RELER: I know where I personally  
18 want to go, and have bundled them in my own mind, but  
19 then I reran the questions relative to the bundles,  
20 and so I know how to answer the questions  
21 sequentially.

22 So I can go either way. It will get to  
23 the same place.

24 DR. TUAZON: I would second their motion,  
25 because I think that pretty much they are going to be

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1       obsolete.

2                   CHAIRMAN WILSON:   Okay.  Then the motion  
3       and the second, is to vote on these as one bundle  
4       grouped together.  Any other discussion on that before  
5       we vote?

6                   DR. NG:   I don't understand why we are  
7       making this motion.

8                   CHAIRMAN WILSON:   Go ahead, Dr. Ng.

9                   DR. NG:   I feel that we won't be worse off  
10       than we have been for the last 50 years.

11                   CHAIRMAN WILSON:   Okay.   Any other  
12       comments?  All right.  All in favor of the motion  
13       raise your hand, please?

14                   MS. POOLE:   So that is four out of seven  
15       voted yes to bundle; and before we go any further, our  
16       voting members today are Kathleen Beavis and Marge  
17       Smith, and there were five members who have voted as  
18       temporaries pursuant to the authority granted under  
19       the Medical Device Advisory Committee Charter, dated  
20       October 27th, 1990; and as amended, August 18th, 1991.

21                   And I appoint the following persons as  
22       voting members of the Microbiology Devices Panel for  
23       the duration of this panel meeting on March 7th, 2002:  
24       Irving Nachamkin, Valerie Ng, Barth Reller, Laura  
25       Thrupp, and Ronald Zabransky.

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1                   For the record, these people are special  
2 government employees, and are either a consultant to  
3 this panel, or a consultant and voting member of  
4 another panel under the Medical Devices Advisory  
5 Committee.

6                   We have undergone the customary conflict  
7 of interest review, and we have reviewed the materials  
8 to be considered at this meeting, and it is signed  
9 David W. Feigal, Junior, Director, Center for Devices  
10 and Radiological Health.

11                   CHAIRMAN WILSON: Thank you. So the vote  
12 was 3 votes to 4, I believe. Okay. Those opposed?

13                   (A show of hands.)

14                   CHAIRMAN WILSON: We have three opposed,  
15 and apparently, Dr. Beavis, are you abstaining?

16                   DR. BEAVIS: No, but I would like to  
17 abstain.

18                   DR. THRUPP: Was that prior to --

19                   DR. NG: Can she second my motion, because  
20 if she can't second it --

21                   CHAIRMAN WILSON: Technically, no, you are  
22 right. She cannot. That's right. She is not a  
23 voting member.

24                   DR. NG: Then my motion has not been  
25 seconded.

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1 CHAIRMAN WILSON: Okay. So we have a  
2 motion then and do we have a second?

3 DR. SMITH: Yes.

4 CHAIRMAN WILSON: We have a second. So,  
5 let's redo the vote then. All of those in favor of  
6 the motion, signify so by raising your hand?

7 (A show of hands.)

8 CHAIRMAN WILSON: Okay. Those opposed?

9 (A show of hands.)

10 CHAIRMAN WILSON: Okay. The motion  
11 carries.

12 MS. POOLE: There are four for bundling  
13 and three against bundling.

14 CHAIRMAN WILSON: So then we will do it as  
15 a bundle group thing. Dr. Thrupp.

16 DR. THRUPP: If I could just mention that  
17 the reason that I was not in favor of bundling was  
18 that the epidemiologic use of antibody testing I think  
19 is in a different order of danger, or safety, and  
20 effectiveness compared to the direct clinical testing  
21 and that's why I was thinking that we could handle the  
22 antibody testing separate from the antigen detection,  
23 the phage, and the FA.

24 You can bundle or advise on the FA if you  
25 want, but I think the others should be separate.

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1 CHAIRMAN WILSON: Okay. So we will go  
2 ahead and proceed then with the vote. The first  
3 question again then is the in vitro diagnostic product  
4 or the information derived from its use potentially  
5 hazardous to life, health, or well being, when put to  
6 its intended use. So would anyone like to make a  
7 motion on that?

8 DR. THRUPP: Yes.

9 CHAIRMAN WILSON: Dr. Thrupp.

10 DR. THRUPP: I move that we answer yes.

11 CHAIRMAN WILSON: Do we have a second?

12 DR. NACHAMKIN: I move.

13 CHAIRMAN WILSON: Any discussion? Could  
14 you give your reasoning for that, Mr. Thrupp?

15 DR. THRUPP: I think post 9-11 is enough  
16 reasoning, a major bioterror agent, and handling of  
17 facilities for diagnosis and public health response,  
18 and clinical response, is critical information.

19 And can be hazardous not only to  
20 individual health, but to the public's health if such  
21 tests are not performed appropriately. All right.  
22 Any other comments? We have a motion and a second.

23 And so all in favor, please signify by  
24 raising their hand?

25 (A show of hands.)

1 CHAIRMAN WILSON: Any opposed?

2 MS. POOLE: Okay. It was unanimous.

3 CHAIRMAN WILSON: Okay.

4 DR. RELLER: Do we actually when we are in  
5 the yes and no category, as opposed to the  
6 descriptions, and let's say we were to come to  
7 limitations, or restrictions, or wherever, where we  
8 would need something specific to vote on, on yes-no,  
9 doesn't that just mean that we can vote yes or no?

10 I mean, we are ending up in the same  
11 place. If we have a motion to vote yes, then it is  
12 yes or no. So we could truncate that process.

13 MS. SCHULMAN: That's fine on however you  
14 would like to do it. You could read each question and  
15 then after each person said yes or no, and --

16 CHAIRMAN WILSON: We are just repeating  
17 that for the public record, and have people state some  
18 of their reasons for why they are making a motion or  
19 not.

20 MS. SCHULMAN: That's fine. That's  
21 absolutely fine.

22 CHAIRMAN WILSON: And I would ask again,  
23 ask the panel members as we go along to please  
24 complete their forms, okay?

25 Now, the second question then is there

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1 sufficient information to determine that general  
2 controls are sufficient to provide reasonable  
3 assurance of the safety and effectiveness of the  
4 device, or in this case, of the devices. Dr.  
5 Nachamkin.

6 DR. NACHAMKIN: I have a motion to vote  
7 no.

8 DR. THRUPP: Second.

9 CHAIRMAN WILSON: Any discussion or any  
10 comments? Dr. Nachamkin, do you just want to comment  
11 on your thinking there?

12 DR. NACHAMKIN: Well, I think there has  
13 been plenty of discussion to support the content that  
14 these are fully characterized, and the procedures are  
15 not well standardized.

16 Clearly if they become available to  
17 laboratories, regardless of their level A or level B,  
18 they need strict controls, and guidelines on how these  
19 tests should be performed, and that is the basis for  
20 that.

21 CHAIRMAN WILSON: Okay. Any other  
22 comments from the panel members? Okay. We have a  
23 motion and a second to vote no on that. All in favor?

24 (A show of hands.)

25 CHAIRMAN WILSON: Okay. It is a unanimous

1 vote. All right. Now, the implications of that vote  
2 are that we cannot classify this as a Class I device,  
3 which means that we go on to Question Number 3, or  
4 3(a), and that is that considering the nature and  
5 complexity of the product, and the available  
6 scientific and medical information, is there  
7 sufficient information to establish a special control,  
8 or set a special control to provide reasonable  
9 assurance of the safety and effectiveness of the  
10 device. Dr. Ng.

11 DR. NG: I move that we vote yes.

12 DR. SMITH: I second.

13 CHAIRMAN WILSON: Okay. We have a motion  
14 and a second. Dr. Ng, what is your thinking behind  
15 that?

16 DR. NG: I think we heard around this room  
17 a number of recommendations that were made to ensure  
18 to test the performance as well as it possibly could,  
19 including restricted access, including level of  
20 expertise, et cetera.

21 CHAIRMAN WILSON: Okay. Any other  
22 comments? And I just want to make it clear that if we  
23 vote yes on this question, we will be recommending  
24 that we classify this as a Class II device. Okay. We  
25 have a motion and a second. All in favor?

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1 (A show of hands.)

2 CHAIRMAN WILSON: Opposed? Okay. It is  
3 unanimately approved. Okay. As the vote was yes,  
4 proceed to question number 3(b), which is to check the  
5 special controls needed to provide such reasonable  
6 assurances.

7 In this case, I think we can handle this  
8 by -- well, rather than -- well, obviously we will be  
9 saying that we need those things, and it is not really  
10 a yes or no vote as indicated on the form.

11 I think in this case what we would like  
12 would be motions for those special controls that  
13 people think are needed. So I would like to open it  
14 up for those suggestions at this time. Dr. Reller.

15 DR. RELLER: In broad terms, I think all  
16 three of these products for some of the same for some  
17 different reasons, the phage one needs a living  
18 organism, and I would like to see all living organisms  
19 confirmed in addition to what the reporting  
20 requirements are, being in the hands of a public  
21 health laboratory for lots of reasons.

22 And for the organism to do molecular  
23 typing, sameness, tracing, epidemiological, et cetera.  
24 The antibody. I don't think any of these tests are  
25 necessary in a front line laboratory to be able to

1 and coupled with clinical assessment of the patient,  
2 necessary to initiate care.

3 I think when we have one of these  
4 organisms, there is or there is the potential to have  
5 a public health issue. And when we come to the  
6 antigen, especially there, I don't think that antibody  
7 testing is something that is going to be useful on the  
8 front line.

9 So it seems to me that all three of these  
10 tests should be -- that it requires -- from what we  
11 have heard, to have them mean something and to be  
12 helpful, they need to be done properly. The  
13 likelihood of them being done we hope is infrequent,  
14 and I don't think that Level A laboratories should  
15 necessarily be excluded, but from what we have heard,  
16 they would need special training.

17 And consequently who is going to supervise  
18 and who is going to be in the capacity to train. Is  
19 this an issue for CAP, or is it an issue for JCAHO, or  
20 is it an issue for -- you know, who is going to  
21 certify that they are properly trained. It seems to  
22 me that the certification could come from the public  
23 health laboratories.

24 So what I would like to move is that with  
25 whatever language that we come up with, and this is

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1 maybe not our job, but the agency's, is that I think  
2 that the distribution and availability of all three of  
3 these products should be in the public health arena.

4 And the extension beyond that be to  
5 designated laboratories that are, if you want,  
6 certified, deputized, trained by, included in, an  
7 expanded laboratory response network.

8 In other words, the details of that would  
9 be to be worked out in the context of the fiduciary  
10 trust that the nation gives to the public health  
11 infrastructure to have these reagents utilized  
12 properly.

13 CHAIRMAN WILSON: Dr. Nachamkin.

14 DR. NACHAMKIN: I generally agree with  
15 Bart's comments, except that I would want to make sure  
16 that it specifically says in the language that level  
17 A laboratories are not excluded from performing the  
18 tasks.

19 Again, it could be worded such that it is  
20 interpreted as only public health laboratories, in  
21 which case I am concerned that the public health  
22 sector really would not step forward to make it  
23 available under specific conditions.

24 So just as long as we are very explicit  
25 and say that laboratories are not excluded.

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1 DR. RELLER: Well, it's not -- well, I  
2 think we are on the same page here, but it is not my  
3 intention by this motion at all to exclude level A  
4 laboratories, but that they be included in the context  
5 of the regulatory, et cetera, that assures proper  
6 training, but assuring proper training and -- you  
7 know.

8 And it is also a distribution and  
9 accountability, and who gets what, and who is trained,  
10 and who is certified, and all of those things that is  
11 under the purview of the public health laboratories.

12 MS. SCHULMAN: Marjorie Schulman. I just  
13 wanted to clarify, too, that we are going to get into  
14 this, and this is going to be more on the restrictions  
15 of the device, which is on the back of the form; as  
16 opposed to the special controls, such as guidance  
17 document, certain labeling, and things like that.

18 CHAIRMAN WILSON: Yes. Dr. Smith.

19 DR. SMITH: I just wanted to echo just  
20 what you said, and just to remind you that the  
21 District of Columbia does not have a State lab. So we  
22 are sort of in a unique position, and I want to remind  
23 people where the epicenter was.

24 And if it happens again, one would think  
25 that it would still be in that area.

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1 CHAIRMAN WILSON: Send them to the FDA.  
2 Go ahead.

3 DR. BROWN: Edward Brown, USAMRIID. At  
4 this point, maybe I am saying things that are already  
5 obvious to you, but not obvious to me. As I  
6 understood it, what you are voting on is sort of the  
7 concept of this assay.

8 I hope that we don't get into a situation  
9 where we would bring in later data to indicate such a  
10 high reliability of the assay that you would have  
11 already put in place special controls that follow-up  
12 devices may appear during the hybernization, which  
13 would not require the sort of special controls and  
14 high complexity training that interpreting a  
15 bacteriological plate would have. I just wanted to  
16 make that comment.

17 CHAIRMAN WILSON: Dr. Beavis.

18 DR. BEAVIS: Thank you for your comment,  
19 but for me that address exactly why I think there need  
20 to be restrictions now. We have been presented with  
21 things, and we have been told that the phages  
22 described in the articles we received are not the ones  
23 currently being used.

24 That the methodologies are variable, and  
25 it is more my uncertainty with what we are being