1 the problems associated with the technology that you might
2 be using.
3 COL. HENCHAL: I appreciate that question because
4 that is one of the plans for one of our hospital studies.
5 Even in the face of no disease for some of these, they will
6 be collecting specimens from similar syndromes. Most of the
7 classical agents can be broken out on a syndromic basis.
8 You can take non-specific pneumonias and include those as
9 part of a test protocol for plague, for example, and we
10 certainly have that as one of our studies.
11 DR. NOLTE: That is useful but it wouldn't
12 necessarily have to be from patients with similar syndromes.
13 There you are sort of getting more into the biological
14 cross-reaction. I am more concerned that the laboratory can
15 do 100 or 1000 of these tests on normal serum and get, you
16 know, negative results so the false-positive rate is
17 attributable to just performing the test --
18 COL. HENCHAL: Precision, right?
19 DR. NOLTE: Well, it wouldn't be precision; it
20 would be false-positive rate.
21 DR. WILSON: That is one possible clinical trial
22 that you could do, specificity studies of trying these out
23 in patients out there because if you proved that your false-
24 positive rate is low, it doesn't answer the sensitivity
25 issue but at least you would have half of the picture. So,

1 these types of trials would be doable.

2 DR. BARON: With positive controls in the mix.

3 COL. HENCHAL: Of course.

4 DR. BARON: So, the chance of cross-contamination

5 is high.

6 DR. MEYER: Right.

7 COL. HENCHAL: Absolutely.

8 DR. WILSON: Any other questions or comments about

9 the first question?

10 DR. NOLTE: One more and then I promise to shut

11 up.

12 DR. WILSON: Oh, don't!

13 [Laughter]

14 DR. NOLTE: I am sitting here, listening to the

15 animal model thing. In principle, I agree that that is very

16 important, but the practicality of it with many of these

17 agents is problematic, from listening to our experts talk to

18 us. And, I would hate to get dogmatic about this in terms

19 of making recommends that, you know, animal model data has

20 to be part of the submission. Clearly, where it is

21 reasonable to do so, I think that should be part of it but,

22 I mean, considering the safety concerns of working with

23 these agents and you are talking about doing animal model

24 studies, you can't use modified agents and I am a little

25 worried about you, guys, doing those studies.

1 COL. HENCHAL: In fact, that is going to be
2 certainly an issue for any of the tests for small pox --
3 DR. MEYER: Absolutely.
4 COL. HENCHAL: -- where the ability to be able to
5 do even animal studies to validate the tests is going to be
6 almost impossible.
7 DR. MEYER: But we are very happy that you are
8 concerned about us.
9 [Laughter]
10 DR. WILSON: Further questions or comments? If
11 not, let's move on to discussion of the second question,
12 which is to determine or infer effectiveness for these
13 devices, can specimens from naturally- or experimentally-
14 infected animals be used when appropriate specimens from
15 humans cannot be obtained? What are the
16 constraints/limitations for us of the animal data?
17 We have talked somewhat about this. I think that
18 one of the specific things that would be helpful to CDC and
19 the Department of Defense is, is this ever going to be an
20 acceptable surrogate for human data? As we have talked
21 about it, they are not perfect but they are the best we
22 have, and I think one thing that might help them is if there
23 are any specific recommendations about types of animal
24 models or the amount of data that can be done so that they
25 can plan for these type of studies. Any comments on

1 specific recommendations? Dr. Baron?

2 DR. BARON: I am a little concerned about the

3 animal models just in terms of public perception of using

4 these animals for this use. It is bound to get out, I

5 guess, don't you think?

6 COL. HENCHAL: Especially after this meeting!

7 [Laughter]

8 DR. BARON: At Wisconsin they used to do

9 tuberculosis model in a rabbit, and what they would do is

10 stand the rabbit up on his hind legs in the cage so that he

11 would be more like a person when he was breathing in the

12 tuberculosis aerosols. So, I think if you could start with

13 lower level animals and do as Dr. Durack suggested, do all

14 your preliminary animal model things with the least

15 objectionable animal.

16 DR. WILSON: Dr. Ng?

17 DR. NG: I would say the literature you provided

18 on looking at aerosolization and longevity of bacillus

19 spores in the air on the monkey model, I believe -- I

20 thought that was an excellent study looking at

21 dissemination. I think those are great studies for anything

22 else you might consider could be disseminated aerosolly.

23 Having been in this field for many years and followed many

24 animal model systems for many different infections, I

25 personally don't think there is an animal model that would

1 ever meet my requirements for what I would want to see as a
2 surrogate for a human study, and knowing that you cannot do
3 human studies for the majority of these, I would be willing
4 to settle for many of these aerosol dissemination studies
5 coupled with culture isolates and defined genetic elements
6 that can be found in the organism that do not require human
7 activation, if that is not part of your detection system.
8 COL. HENCHAL: Let me make sure I understand your
9 comment. Are you saying that you don't think we need as
10 much emphasis on the animal studies, or are we back to
11 reasonable animal studies?
12 DR. NG: I would actually leave that to your
13 judgment. I think the animal studies that you gave us
14 showed more of what happens with the organism when you
15 disperse in the air versus what it does to the animal. I
16 think if you are going to try to develop an animal model
17 system to look at disease and pathogenesis -- I am sorry, I
18 could be wrong but I have yet to see an animal model that
19 really mimics humans. I was even going to say should you go
20 to a SCID mouse, but even that is not adequate. So, in that
21 regard, I don't think you could ever find an animal system
22 that would meet our requirements to mimic the human
23 situation.
24 For example, look at the things you have suggested
25 -- immune markers. You know, the plasticity of the human

1 immune system, ethnic and gender variations in responses --
2 I don't think you can develop an animal model to address
3 those.
4 DR. WILSON: Dr. Hammerschlag?
5 DR. HAMMERSCHLAG: Well, if you look at it sort of
6 a different way, not so much that you are trying to come up
7 with a simulacrum of human disease but if you are interested
8 in, for instance, how these tests perform in different types
9 of specimen in tissue, a model may be helpful in that
10 situation in terms of providing at least infected tissue so
11 you can deal with the factors in tissue certainly with
12 amplification test inhibitors etc. that might interfere with
13 function. That might work somewhat better than spiking
14 human secretions. I don't think you are going to get many
15 people donating livers, and just adding it is not the same
16 as actually having it growing in a living organism's liver.
17 DR. DURACK: Actually, just to reinforce that and
18 agree with it, some of the problem might be in the use of
19 the word "model." Model implies that it is a copy or a
20 surrogate. What the animal does is give you a specimen and
21 I think we should get away from the idea of using it as a
22 model of human disease and say this is a tool in the early
23 stages of product development where you can compare tests.
24 COL. HENCHAL: Yes, we recognize at USMRIID that,
25 for example, spiking whole blood is really not a great model

1 because, for the most part, these organisms actually end up
2 in macrophages and are not freely floating in the
3 circulation. So, we recognize that you do have to be very
4 careful about spiking experiments as a method of validation.
5 DR. NOLTE: That is a reasonable way to maybe get
6 a handle on the analytical sensitivity of the assay, but it
7 really doesn't address the clinical sensitivity and how it
8 might perform as a diagnostic.
9 DR. MEYER: Right, but I think it helps quite a
10 bit in determining how the assay performs in background --
11 DR. NOLTE: Yes.
12 DR. HAMMERSCHLAG: But that may be truly
13 irrelevant. I mean, if we are dealing with something like
14 anthrax, if it s there it shouldn't be there. So, it is not
15 like you are dealing with an infectious setting where there
16 is a large reservoir in people asymptomatically infected.
17 DR. BARON: You didn't mention whole blood as a
18 specimen, but I am wondering why you are not looking at
19 whole blood. You are talking about serum and plasma where
20 there is a lot of manipulation involved and you are putting
21 laboratory people at risk dealing with it.
22 DR. MEYER: The reason we are looking at serum is
23 because the most likely scenario for us would be blood
24 collections. Remember, these are going to be initial blood
25 collections that will be taken and serum will be isolated

1 from the patient specimen initially. So, that will be the
2 type of specimen most likely that we will be looking at. It
3 doesn't preclude looking at whole blood. We plan to look at
4 whole blood but at least initially we are using serum.
5 DR. WILSON: Are there any other questions or
6 comments on the second question?
7 [No response]
8 The third question, are there issues not addressed
9 by the described types of data and information that would
10 impact on the reliability of using these assays for evidence
11 of human exposure or infection? Dr. Nolte?
12 DR. NOLTE: I am not sure I know what that third
13 question means but I am going to comment anyway --
14 [Laughter]
15 I have heard several of the speakers today refer
16 to the fact that, you know, the likely threat is one that we
17 don't know about yet. That raises a rather interesting
18 question in terms of validating tests. Clearly, you can't
19 prepare for the unexpected but looking at an intermediary
20 sort of thing, what happens about genetically modified
21 targets, looking at the degree of manipulation that occur to
22 a candidate target gene or antigen that would still allow
23 detectability? Is that a concept that we need to think
24 about or talk about?
25 COL. HENCHAL: You know, there is a part of the

1 guideline requirements to look at the performance of assays
2 under different conditions of temperature and physical
3 conditions, but your point about how much, for example,
4 generic variation can go on a gene and you still detect it
5 is still an interesting concept that I don't think I have
6 addressed in our program yet. So, that is an interesting
7 idea.
8 DR. BARON: Well, actually, I thought you
9 addressed it very well because you talk about virulence
10 factors. If you modify the virulence factor you don't have
11 a virulent organism anymore.
12 DR. NOLTE: Yes, presence or absence for the most
13 part. Certainly, if you are looking for a virulence factor,
14 you know, that is not there, the organism may not be
15 virulent. But how much variation in that target or
16 modification in that target and how much the assay could
17 stand would be interesting. I don't know whether it would
18 be a requirement for a product. It certainly is something
19 that would pique my interest.
20 DR. MEYER: I think if you use the case of
21 anthrax, for example, one of the things that we have built
22 into our assay is not only detection but, particularly with
23 anthrax, it is important to determine whether you are
24 dealing with a pathogenic strain or with a non-pathogenic
25 vaccine strain, and that can be easily done.

1 DR. WILSON: Dr. Stewart?

2 DR. STEWART: One of the questions that was raised
3 earlier, I believe by Dr. Specter, was what if you had a
4 modified influenza? The question could be applied to other
5 things as well. What if a virulence factor was added to
6 ordinary chicken pox? Obviously, you are not building
7 detection systems for the hundreds of viruses there are, but
8 what would be your response if we found seven or eight
9 deaths due to something that normally does not cause that in
10 a small geographic area?

11 COL. HENCHAL: In fact, I point back to the West
12 Nile strain because actually that was exactly the case where
13 we started to see deaths in an area and with a virus that we
14 had not expected.

15 But I just want to make one other point. I was
16 thinking about what you said, Rich. You know, the mere
17 presence of virulence genes does not mean that that organism
18 is virulent because there could be modifications that don't
19 allow expression or correct expression. There are also
20 cases where people have attempted to put plasmids,
21 especially the plasmids of Bacillus anthracis, in other
22 organisms and, you know, you may find that gene but it may
23 not be related to virulence. So, we do have to be cautious.
24 I raise a precaution about your interpretation, with all due
25 respect, but, yes, I think it is more likely that we are

1 going to find, especially in the emerging disease category,
2 the emergence of infectious diseases that are causing
3 unusual deaths where they would not ordinarily be expected.
4 And, that is the importance of doing good epidemiology, and
5 having a good reporting system, and having a system of
6 laboratories that can communicate and do the analysis.
7 DR. MEYER: I think you all have an appreciation
8 for how many organisms we are talking about. So, what do we
9 do? We either do nothing or we try to build capacity, and
10 building capacity is not something that is going to happen
11 overnight. It is going to be a slow process and it is
12 putting up one brick up at a time, you know, until you end
13 up with a wall or a house.
14 DR. WILSON: Dr. Baron?
15 DR. BARON: I would just like to make another
16 comment about your infective dose data that you provided for
17 us. I would tend to not put my faith in the infective dose
18 being as high for some of those agents as you say because we
19 used to say the infective dose for Salmonella was quite high
20 and then we started seeing these cases of food-borne
21 Salmonella and we realized that the infective dose was more
22 like 10, more like Shigella than what we had said.
23 So, I think you ought to be gearing for a low
24 infective dose, particularly with a genetically altered
25 agent. I would think the dose is going to be real low.

1 COL. HENCHAL: Just to comment about the
2 infectious dose data that has been reported, there have
3 really only been a few really systematic studies to look at
4 the infectious dose for humans, and most of those were done
5 in the old offensive program and have been well documented.
6 For most of the other agents that were not part of that
7 original testing program, those are very often
8 extrapolations from animal models. So, you are absolutely
9 correct. We do have to take a certain amount of that data
10 with a grain of salt.
11 But I should mention that I don't think that is
12 going to have a big impact on validation of assays because,
13 as I think Rich and I agree, we are going to develop the
14 most sensitive assays that we can regardless, and whatever
15 that is, that is what it is going to be.
16 DR. WILSON: Dr. Durack?
17 DR. DURACK: On question three, issues of impact
18 on reliability, I would like to just say a word about
19 specimen handling, preparation and concentration. It has
20 been mentioned briefly. We all know it is terribly
21 important. But when we look at development of new tests
22 over the last decade or so, quite often you see a test is
23 developed and then attention is turned to specimen handling
24 and preparation, and it turns out that that is as big a
25 problem than the test itself.

1 COL. HENCHAL: Certainly.

2 DR. DURACK: So, I think certainly we want robust
3 and reproducible and standardized and simple specimen
4 handling, concentration, transport and storage systems as
5 early as possible, at least in parallel with the test if not
6 before. Of course, sometimes you find out that now your
7 test requires something different. So, it doesn't always
8 work but certainly it has a major impact on reliability.
9 Historically it has turned out to be often difficult and
10 important to standardize those as early as possible, and
11 certainly for the military and mass exposure situation the
12 more standardized it is, the better.

13 DR. WILSON: Dr. Specter?

14 DR. SPECTER: We have dealt with a lot of issues
15 but I don't really feel that I have heard, or at least I
16 don't understand what we really need to be talking about,
17 and that is, in light of difficulty in obtaining clinical
18 specimens to do the testing, what is a sufficient substitute
19 for doing the testing that would routinely be done to
20 satisfy the FDA? And, I haven't heard any recommendations
21 that address that yet and I think that is a major thing we
22 need to be dealing with here -- what do we do when we can't
23 get the specimens? Or, what advice do we give them for what
24 they need to do when they can't get the clinical specimens?

25 DR. WILSON: Comments?

1 DR. NOLTE: I think we have been talking about
2 that, haven't we? We have been talking about animal models
3 where appropriate. We have been talking about spiked human
4 specimens.
5 DR. SPECTER: I guess what I am getting at is I
6 heard pros and cons about using animal models but no real
7 consensus or feeling about it. I have heard statements that
8 spiked specimens aren't very good. While they may not be
9 very good, I don't know what the alternative is to them if
10 you don't use them. So, I would like to hear something that
11 is more a consensus as to, well, this could be good and this
12 could be bad. I am not walking away feeling that we have
13 said anything that is guiding. We have just said things are
14 out there and they can be used but, you know, do what you
15 want and I don't think that is what we are here to do. I
16 think we are here to give some specific guidance as to
17 alternatives to using clinical specimens.
18 COL. HENCHAL: Sir, do you think that we need to
19 have guidance for a select group of agents? I am not sure,
20 and in some ways I agree with you but you could only give
21 broad guidance here because of the number of agents that
22 must be addressed. It may be incumbent upon people like
23 Rich and me to justify in our submissions the specimens that
24 we are going to use to do our validation. For example, we
25 might have to justify an animal model, or we may have to

1 justify a spiked sample system. I don't know how to deal
2 with that unless we get specific guidance for each agent.
3 DR. HAWKINS: It seems to me that if we are saying
4 that animal models are not perfect and spiking is not
5 perfect, then we need to be doing both. Isn't that our
6 guidance?
7 DR. SPECTER: Well, I think they are going to
8 vary. I mean, there are going to be certain things where
9 there aren't animal models or you are going to have to
10 create an artificial animal model, and is that a valid way
11 to go about doing this? And, it may be if it is the only
12 thing you can do.
13 DR. MEYER: Well, i think that is the point. I
14 think, you know, there is a limit to what you can do and so
15 you have to decide upon, out of what is available, which way
16 you are going to go, or are you going to encompass
17 everything that is available and utilize that as data
18 generation.
19 DR. HAWKINS: But, surely, within reason we want
20 to use as many different views as we can and, to the extent
21 that they tell a consistent story, be comfortable with the
22 results.
23 DR. MEYER: I think one very good suggestion that
24 Dr. Nolte made before was to take a look at a fairly large
25 number of "normal" material to make sure that none of that

1 material causes a problem or gives us a false positive. I
2 think that is a good way to start, obviously.
3 DR. WILSON: Dr. Gutman, I might just ask you to
4 interject whether you think we are giving sufficient
5 guidance to FDA.
6 DR. GUTMAN: Yes, I actually think that there has
7 been a lot of useful information here, and I actually think
8 that there are answers even in the questions you don't
9 answer in that there are limitations to what you can do.
10 But I think there has been a wealth of insights here. In
11 general, in our review process, we are looking for least
12 burdensome thresholds and wouldn't want to apply anything
13 more than least burdensome to our colleagues in another
14 government agency, particularly under the circumstances.
15 So, for example, the concept of looking hard at the animal
16 model and making sure it provides some value is one that I
17 am taking away. I don't think we should require animal
18 studies unless they do provide insight into samples or they
19 do have some parallel to humans, otherwise why do it? Don't
20 do data that has no meaning.
21 You did not mention, for example, when you are
22 doing point of care studies -- we have been playing around
23 with the CLIA program and when they extrapolate they
24 deliberately do their reproducibility studies and
25 extrapolate performance in the hands of general users, using

1 artificial samples because they don't want to expose
2 untrained people, frankly, to hazards that are much less an
3 issue. Maybe I didn't ask because I had preconceived
4 notions about that based on our use of the CDC program.
5 But I certainly wouldn't oppose something more
6 concrete. I appreciate Dr. Specter trying to make an honest
7 panel --
8 [Laughter]
9 -- but, in fact, you can only do what you can do
10 and we did expect this to be a general discussion and we
11 didn't expect you to reach consensus. We expected you to
12 provide a variety of insights. If you have other insights,
13 we would like to have you share them with us. You don't
14 have to give us all the answers today. You can go home and
15 think about it and send Claudia, Roxanne or Freddie an e-
16 mail or comments post-panel. These are really difficult
17 issues. And, I think one of the things -- maybe we shot
18 ourselves in the foot -- that does make this hard is that
19 there is such a wide menu of possible pathogens, some better
20 established than others. For some there may be actual banks
21 of samples to call on. So, I am not sure one size fits all.
22 DR. SPECTER: If I could make a comment?
23 DR. WILSON: Yes.
24 DR. SPECTER: The one thing I would like to leave
25 with is Dr. Baron made the point about testing a broader

1 number of organisms for cross-reactivity that may lead to
2 false results. In that regard, one of the things that I
3 would like to suggest very strongly -- and it probably
4 pertains to all manners of testing -- is providing the
5 rationale for why you did one set of organisms or one thing
6 versus another.
7 I just had the experience of going through
8 something in which a whole battery of organisms were
9 presented for cross-reactivity and I have no clue why they
10 tested many of those organisms, and why they chose not to
11 test a closely related organism to the one that was the
12 assay organism. So, you know, if you provide a rationale
13 for why you did these things it really makes it easier to
14 evaluate what it means, and I would hope that if you are
15 going to pick spiked specimens versus animal models, or
16 whatever, that you provide the rationale why you went that
17 way so that when you go to evaluate it we know what you were
18 thinking and can say this makes sense or it doesn't.
19 DR. NOLTE: I would like to make a comment on that
20 too because, especially if you are moving toward nucleic
21 acid technology, the concept of blindly testing every
22 microorganism that you can put your hands on is a bit
23 antiquated. I mean, searching data bases for gene homology
24 is probably the way to go and then making some intelligent
25 choices about doing that testing rather than, you know,

1 picking willy-nilly which seems to find its way into a lot
2 of these specificity trials. And, I don't know how the FDA
3 feels about that.
4 DR. GUTMAN: Well, we are supposed to look at the
5 least burdensome. So, I think all these points are well
6 made. We shouldn't be asking scientific questions unless
7 they are reasonable questions that will provide insight,
8 frankly, into the core of whether a product is safe and
9 effective. The Army and the CDC can go as far afield as
10 they want in interesting academic pursuits but when they
11 bring a product to us -- now, this is a particularly
12 difficult focus here --
13 DR. NOLTE: True.
14 DR. GUTMAN: -- and it may not be easy. One of
15 the questions is when you reach the threshold of actually
16 saying you have enough data, frankly, to move it from an
17 investigational to an approved state. If, and when, we
18 reach that point, that may be quite challenging. Maybe
19 there are some products that don't ever deserve to be
20 approved. They are just investigational because you can't
21 do any better than that. They have a lot of expertise in
22 this so maybe they will help us, but we are supposed to keep
23 the issues focused on what is relevant to defining
24 performance, not what is interesting.
25 DR. NOLTE: Sure. But one other point that I

1 guess is obvious but I will state it anyway, the reagents
2 they are working with here represent significant threats to
3 people who handle them, and work with them, and are doing
4 the testing. So, I guess I would be really interested in
5 seeing the data on the inactivation of the controls, maybe
6 more so than a standard test that comes through the FDA.
7 DR. WILSON: And I think along that same line of
8 thought, these tests will, hopefully, be used infrequently.
9 There should be little need, yet, one will need to maintain
10 proficiency and competency. So, I think one thing that
11 would be of interest would be to see what sort of
12 proficiency testing you can develop, again, in light of the
13 fact that you can't be sending the actual isolates out.
14 But along the same lines, a couple of pieces of
15 data that I think would be necessary is that because they
16 won't be used that often in that many places, you would need
17 some pretty good data about inter-user variability because a
18 lot of tests are very user dependent. And, also shelf life
19 and storage because as you move down the line to point of
20 care testing, these things may well end up in areas of
21 changing environmental conditions and everything else. So,
22 I think we would want to know, at least for a reasonable
23 period of time, whether these things continue to work.
24 DR. GUTMAN: But the issue -- actually it is again
25 a double issue, as Dr. Specter brought up -- the issue about

1 getting the right samples to study, looking for the things
2 that you think will interfere and not worry about the things
3 that won't interfere, obviously requires some up-front
4 thought about the design of the experiment, and having
5 appropriate rationales or justifications for deciding what
6 you are going to study and what you are not going to study,
7 and what data sets you are going to present and what data
8 sets you are frankly not going to worry about. That is part
9 of the game here that is actually critical to an intelligent
10 submission. God knows, lots of sponsors, in fact, make
11 arguments about what data sets are relevant and not
12 relevant, and we are prepared to negotiate that with these
13 folks. And, frankly, if there are questions on specific
14 products, then come back to people here who might have
15 something to contribute.
16 DR. WILSON: Dr. Stewart?
17 DR. STEWART: I have a question. We are
18 accustomed to saying "for research use only" or "for in
19 vitro." Are we going to have a third category here?
20 DR. NOLTE: For emergency use only!
21 DR. GUTMAN: Well, we are not going to worry about
22 that today. We want to talk about the science of
23 submissions, and we are not planning to create special
24 categories but we will --
25 DR. STEWART: We will try and keep this in the

1 research area.

2 DR. GUTMAN: Well, we will try to make sure that

3 the shoe fits.

4 DR. WILSON: Additional comments or questions?

5 DR. MEYER: I like that special category.

6 [Laughter]

7 DR. WILSON: If there are no further comments or

8 questions, I would like to move now to the second open

9 public hearing. If anyone has any comments or questions,

10 please come to the microphone and please identify yourself.

11 **Open Public Hearing**

12 MR. SAWICKI: My name is Jack Sawicki. I have

13 three short comments and I have a conflict of interest on

14 each one. So, I figure I better say that up front. I work

15 for Geomet Technologies which is a biological/chemical

16 testing facility. We also do development work of

17 biological/chemical detectors and protective systems. I am

18 also the Emergency Medical Services Council chair of

19 Arlington, Virginia. In that role, I have also been

20 appointed to the inter-agency board, DOD, DOJ, for Weapons

21 for Mass Destruction Detection. So, I have a number of

22 different hats. I will try to balance those as I ask these

23 questions.

24 The first one to the FDA is, by their

25 presentations today, should we assume that the only

1 mechanism of submitting a diagnostic or other test to FDA is
2 through CDC or the Army or DOD?
3 DR. WILSON: I am sorry, I don't believe you can
4 ask questions of the panel. I think you can just make
5 comments. Is that right?
6 MR. SAWICKI: Okay. I guess my comment would be
7 it would appear from the presentations today --
8 [Laughter]
9 -- you need to be a lawyer for this! It would
10 appear from the presentations today that industry should
11 assume that we have to go through either CDC or DOD to be
12 involved in this.
13 DR. GUTMAN: I have to answer that because that
14 actually is not at all correct. There is absolutely nothing
15 that would preclude us from interacting with any part of
16 industry. You show the intended use and we will talk to you
17 about what the appropriate regulatory route is.
18 MR. SAWICKI: Okay. The second comment is as a
19 representative of first responders -- I don't think there is
20 anybody else here so I will try to put Chief Ebersol's
21 helmet on. If anybody knows him, it is a hard helmet to
22 fill, but there is a scenario that I think needs to be
23 addressed by the FDA because no one else is capable of
24 addressing it, in my opinion, and that is an unannounced or
25 an announced attack on a large building. I would like to

1 bring one up that Chief Ebersol did in a recent meeting that
2 I attended where you have, for example, the Sears Tower in
3 Chicago, and a terrorist calls up a radio station and says I
4 released anthrax into the HPA system at nine o'clock this
5 morning. You have 10,000 people in the building. Fire
6 department responds. Everybody is called, the FBI, CDC,
7 whatever.
8 It has been said that clinical tests are the
9 primary thrust of the FDA, and I understand that history but
10 I would urge you to address the concept of how you would
11 validate environmental sample collection and environmental
12 testing and analysis with your clinical tests to give the
13 emergency medical people and the first responders some means
14 of addressing the issue at the scene rather than four hours
15 later or eight hours later. Ebersol's comment was, and I am
16 paraphrasing it, what the hell am I going to tell those
17 10,000 people who are waiting for something else to happen?
18 The problem we have right now is there are many,
19 as I will call them, snake oil salesmen because that, again,
20 is what Ebersol used, that are peddling different kinds of
21 devices to first responders as an answer to that problem,
22 and I think without FDA addressing that, there is a
23 tremendous vacuum there that someone needs to validate for
24 those users, and I don't think the system that is in place
25 right now is capable of doing that. So, I urge you to do

1 that.

2 DR. NOLTE: I am curious, there are people selling

3 products for that purpose now?

4 MR. SAWICKI: Yes, actively and aggressively.

5 DR. HAMMERSCHLAG: And this is being targeted to

6 fire departments?

7 MR. SAWICKI: Fire departments, yes. Fire

8 departments right now are receiving grants from different

9 organizations, from DOJ and DOD -- they are allowed to buy

10 equipment.

11 DR. NOLTE: And these are biological agents?

12 MR. SAWICKI: Yes.

13 DR. HAMMERSCHLAG: And, as far as you know, these

14 haven't been tested or nobody knows about their performance?

15 MR. SAWICKI: There is a degree of testing that

16 has been done to all of them but there is no standard

17 approval or protocol that exists for that. So, the

18 possibility of false positive, false negatives -- there is a

19 tremendous variation in the quality and, as a biological

20 testing laboratory, we know that.

21 The other thing is it is very good to say come in

22 with a bunch of different things and justify where you are

23 going. I think you need some very specific targets for

24 industry to follow on this to give us some guidance in

25 development because I don't see the technology that is out

1 there right now for this field application to be very good,
2 and maybe the Army could comment on that. I think the FDA
3 is probably in a better position than anyone to spur that
4 kind of development, and the best way to do that, in my
5 opinion, would be to give some targets to industry to meet
6 and try to come up with a way of addressing that issue.
7 DR. RELLER: Did I understand correctly that there
8 are government agencies giving grants to enable the purchase
9 of this, or that there are government grants for
10 preparedness and some of the money for the preparedness is
11 being used to purchase these detectors?
12 MR. SAWICKI: Yes.
13 DR. RELLER: So, it is the latter reality?
14 MR. SAWICKI: Yes.
15 DR. RELLER: The end result may be the same of
16 using unvalidated detectors. The mechanism by which this
17 happens though I think is an important distinction. I mean,
18 both are important issues. So, these are grants for
19 preparedness. That is, part of the preparedness people are
20 incorporating or using or considering using devices that
21 have not been validated for detection of environmental
22 contamination or potential exposure of individuals.
23 MR. SAWICKI: Yes.
24 DR. WILSON: Dr. Gutman, I think I know the answer
25 but could you clarify what role, if any, FDA would have in

1 that?

2 DR. GUTMAN: Yes, we actually appreciate these
3 comments and would consider them. There actually is a
4 regulatory gap in terms of what our role might be in
5 environmental testing, and one presumes as these discussions
6 advance that if not our agency, other agencies will take
7 perhaps a heightened interest.

8 MR. SAWICKI: The other issue I would like to
9 address is sample collection more specifically. For
10 environmental samples there is a tremendous variation and
11 tremendous confusion about sample collection, both from
12 aerosol air type sampling or surface sampling or liquid
13 sampling. There really needs to be more standardization in
14 this area and a standardized test for evaluating these kinds
15 of sample collections.

16 I was recently involved with an event as a
17 contractor supporting a law firm, actually, in an issue of
18 unknown release in a hospital emergency room in Riverside,
19 California. Some of you may have seen this on television,
20 but a patient came in and supposedly gave out some kind of
21 mystery element. Two medical professionals went into
22 cardiac arrest at the scene of that particular thing. It
23 was eventually ruled to be hysteria. You know, I would
24 suggest that if you had a building with 10,000 people in it,
25 if you told them, go home; yes, they said it was anthrax.

1 Next morning you would probably have a thousand people with
2 all the symptoms of anthrax that they have gone home and
3 read up on.
4 So, I think we really need to be careful. It is
5 all very well and good to say, okay, we will sample sputum
6 or we will sample whatever, but the building is still there
7 and it is a tremendous problem to try to get a building back
8 into use again, or find out if it can be put back into use.
9 And, I think someone has to address that and I think there
10 is a large regulatory gap in that area as well that FDA may
11 be able to fill. Thank you.
12 DR. WILSON: Dr. Nolte?
13 DR. NOLTE: I guess there are several different
14 ways to think about this, but I got the impression that the
15 Army is thinking about having both environmental testing
16 going on as well as human clinical specimen testing, and
17 that what we have talked about a lot here today was the
18 analytical components of the test, and the analytical
19 components of the test shouldn't differ whether it is an
20 environmental sample that is the input or a clinical sample.
21 So, what we are talking about then to expand the technology
22 is more on the specimen acquisition and preparation. Is
23 that correct?
24 COL. HENCHAL: Are you asking me? What you say is
25 true. There are programs within the DOD that are centered

1 on environmental testing and clinical diagnosis, and some of
2 these programs use complementary technologies. There is a
3 problem in that there are not good standards for processing
4 and evaluating tests related to environmental sampling. So,
5 the speaker from the public was correct in that. I have
6 been hoping that if the FDA is not able to address the
7 impact of environmental sampling some other agency, maybe
8 EPA for example could.
9 But we do recognize that environmental sampling in
10 the hands of the first responder may result in some medical
11 decisions being made in advance of any clinical specimen
12 becoming available, and we are going to need some strong
13 regulatory guidelines. I think the public needs regulatory
14 guidelines especially on the issue of what medical decisions
15 can be made under those circumstances.
16 DR. WILSON: Are there any further public
17 comments? There being none, the open public hearing is
18 closed. We will take a short break now and reconvene in 15
19 minutes if there is any further open committee discussion,
20 to review the questions and make any final recommendations.
21 [Brief recess]
22 **Open Committee Discussion and Final Recommendations**
23 DR. WILSON: For the last part of the open
24 committee discussion, the final recommendations, what we
25 would like to do is briefly review the questions, with a

1 succinct summary of what was stated and recommended. We
2 will then ask each panel member if they have any final
3 comments and we will finish up by asking the guests if they
4 have any unanswered questions.
5 The first question, what types of data and
6 information would be considered appropriate to evaluate
7 safety and effectiveness when these assays are used -- it
8 seems that the consensus was that the four questions, moving
9 from identifying cultures on up to point of care testing,
10 became progressively more challenging from the standpoint of
11 validating the safety and effectiveness of the devices; that
12 one would certainly need to start with the ability of the
13 assays to accurately identify culture isolates; couple that
14 with appropriate cross-reactivity studies. We heard that
15 from several speakers. And, when one has very clean data on
16 that, then one can move more into the performance
17 characteristics, inter-observer variability and so forth.
18 There was a lot of discussion on the issue of
19 sensitivity versus specificity. Obviously, both are very
20 important. The comment was made by a couple of discussants
21 that these tests are not always going to be used in the same
22 sense as a clinical diagnosis test; that the issue of
23 specificity is of paramount importance.
24 As one moves down the chain from (a), (b), (c) to
25 (d), in terms of different types of specimens that might be

1 tested that we discuss the issue of spike specimens, the
2 effect of matrix, specimen collection and processing, all of
3 which are very important.
4 Finally, the last issue that was brought up was
5 the issue of how these tests will actually be used in the
6 field -- their durability, stability, and so forth.
7 Does anyone have anything they would like to add
8 to that regarding question number one? Dr. Nolte?
9 DR. NOLTE: I presume this falls under question
10 number one, I mean, the concept of test panels and test
11 systems versus individual tests I thought was an important
12 point, and the concept of whether they are done as a panel
13 or as tiered or reflexive testing I think is an important
14 issue that we talked about that didn't make it to the
15 summary.
16 DR. WILSON: Good point. Thank you. Any other
17 comments?
18 [No response]
19 The second question is regarding the issue of
20 using naturally- or experimentally-infected animals for
21 models when appropriate specimens from humans cannot be
22 obtained, and what are the constraints/limitations for use
23 of animal data?
24 I think there was realization that animal models
25 may be the best we can do because there won't be any human

1 models for these infections and, yet, that needs to be
2 tempered by the fact that we need to use appropriate animal
3 models, and that when you can use something other than an
4 animal model that would be desirable, but certainly
5 realizing that at times we will have to use the best animal
6 model. There was quite some discussion on that. Does
7 anyone have anything they would like to add to that?
8 [No response]
9 The, the third question, are there issues not
10 addressed by the described types of data and information
11 that would impact on the reliability of using these assays
12 for evidence of human exposure or infection?
13 This is, again, somewhat of an open question. Dr.
14 Gutman has said that people should feel free to submit any
15 information that they think is valid to the FDA after this.
16 I would just ask if anyone has thought of anything during
17 the break that he or she would have like to have brought up
18 at the time, any performance characteristics? Anything else
19 that they think is relevant? Dr. Reller?
20 DR. RELLER: It seems to me that intended use is
21 an important concept to build into these tests. This has
22 been addressed in part before, but in classic
23 epidemiological investigations the initial step is deciding
24 whether or not there has been a cluster or outbreak and then
25 very quickly confirming what the etiology is because the

1 control measures depend on that.

2 I could envision that what we are talking about

3 here is a public health issue or risk where one of the

4 putative sensors, detectors or diagnostics may be has there

5 been an exposure -- yes/no? And, if one has something with

6 very great sensitivity and this is clearly ruled out as a

7 hoax; this is not spores; it is not in the air conditioning

8 system, etc., that would be very important to be deployed

9 quickly.

10 Thinking of Dr. Curtis' presentation and some of

11 the discussion in the public hearing that took place, I

12 mean, I could see these as being exactly the sort of thing,

13 both for the individual as well as for the community, that

14 could be important, and the criteria used to evaluate those

15 would be quite different from the reference laboratory, as

16 was pointed out earlier with whatever it takes to get

17 specimens where they need to get for early confirmation of

18 the exposure so that there may be a product or device that

19 would rule out an exposure, and then the mechanism and the

20 product that would confirm an exposure that could not be

21 ruled out in the first pass. Then you get into the

22 sequential testing.

23 So, it seems to me, there must be a lot of

24 flexibility. Then, whether animals or spiked specimens, and

25 what kind, and the pitfalls depend on what the detection is.

1 Basically, it comes down to the flexibility to look at these
2 things for intended use and then what is available and the
3 capacity on scientific grounds to assess whether the data
4 presented by the sponsor, be it governmental or private
5 sector sponsor, demonstrates efficacy and safety for
6 intended use. And, I think the intended use is a very
7 important issue.
8 DR. WILSON: Thank you. Dr. Stewart?
9 DR. STEWART: It was interesting in terms of West
10 Nile virus, the recent survey that was done to find out what
11 was the extent of exposure and, obviously, that is not what
12 you are dealing with in the initial event but the question
13 is are there are serologic assays that are also being
14 developed to evaluate just how far did this agent go in
15 terms of the type of delivery system that was used and what
16 happened. Are there plans to look at that as well?
17 COL. HENCHAL: Within the DOD we have several
18 immunologically based assays specifically to detect the
19 immune status of individuals. Right now, there hasn't been
20 a plan to bring those to the FDA. They primarily have been
21 used in the context of our vaccine development.
22 Unfortunately, for some of the biological threat
23 agents, patients die before they develop an antibody
24 response and so many of the IgM based tests, for example,
25 have not been very useful, at least in the animal models,

1 because of the short course of disease.

2 DR. WILSON: Dr. Baron?

3 DR. BARON: This may be obvious and we discussed

4 it but you didn't mention it so I will mention it again.

5 Dr. Durack brought up specimen handling, and we are thinking

6 about using these kinds of tests in the field and I think

7 about tropical areas or hot, dry areas. So, I think part of

8 the parameters that need to be addressed are the specimen

9 limitations and handling criteria. So, when you evaluate

10 this tests, I think you need to evaluate them in a hot

11 place, a cold place, specimens that have been hemolyzed --

12 you know, all that sort of thing.

13 DR. WILSON: Good. Thank you. Anything other

14 questions or comments about the third question? If not, I

15 would like to just go around the panel and see if anyone has

16 anything final comments or recommendations they would like

17 to make. Dr. Weinstein?

18 DR. WEINSTEIN: No further comments.

19 DR. WILSON: Dr. Ng?

20 DR. NG: No.

21 DR. WILSON: Dr. Reller?

22 DR. RELLER: No.

23 DR. WILSON: Dr. Specter?

24 DR. SPECTER: No.

25 DR. WILSON: Dr. Baron?

1 DR. BARON: No.

2 DR. WILSON: Dr. Hawkins?

3 DR. HAWKINS: No.

4 DR. WILSON: Dr. Durack?

5 DR. DURACK: No.

6 DR. WILSON: Mr. Reynolds?

7 MR. REYNOLDS: No.

8 DR. WILSON: Dr. Tuazon?

9 DR. TUAZON: No.

10 DR. WILSON: Dr. Hammerschlag?

11 DR. HAMMERSCHLAG: No.

12 DR. WILSON: Dr. Stewart?

13 DR. STEWART: No.

14 DR. WILSON: Dr. Smith?

15 DR. SMITH: No.

16 DR. WILSON: Dr. Nolte?

17 DR. NOLTE: No.

18 DR. WILSON: Then, two final orders of business.

19 First, I would like to ask our guests if they have anything

20 unanswered questions or information they would still like to

21 hear from us at this time.

22 DR. MEYER: I have a question that I think I

23 probably should pose to the FDA, if I am allowed to do that.

24 This has all been very, very helpful and we appreciate and I

25 think both Dr. Henchal and myself appreciate the fact that

1 we had this opportunity to interact and to have these
2 discussions, and I have certainly found them very, very
3 helpful. The question I have is when we leave here today,
4 Dr. Henchal and myself still have the job of getting these
5 assays developed and validated, and my question is that with
6 the recommendations that come out of this advisory panel, at
7 the appropriate time when we conduct these studies and
8 present the data to FDA, who makes the decisions on whether
9 we have all the correct data?
10 DR. GUTMAN: Well, the final decision is actually
11 made by the agency. Depending on the nature of the
12 submission, it might or might not go through this panel
13 again. If it was a particular submission as a potential to
14 bring a specific submission either to the panel for a
15 routine product-related panel meeting. An alternative for a
16 sort of intermediate submission might be to assign that
17 product for homework assignments and have some key members
18 of the panel review but not have a formal panel meeting.
19 And, for some products if you have products that are not
20 first of a kind, or were perhaps 510(k) or de novo 510(k) se
21 might not even seek panel input. It depends to a great
22 extent on what the product is whether the panel is involved
23 or not. It is advisory. So, we get the joy of making the
24 final decision. When we have difficult products, we
25 generally don't do that without panel input.

1 DR. WILSON: Dr. Durack:

2 DR. DURACK: Actually, I have a question for Dr.
3 Gutman as well.

4 DR. GUTMAN: Can I amend the question because it
5 is important to us actually. You folks here, the guests in
6 particular, are obviously in the center of ownership in
7 terms of scientific issues and understanding the products.
8 That is not to suggest there might not be people in the
9 private sector who might have an interest and might be able
10 to contribute, but you certainly are right at the front of
11 the list. It is our intention to work with you in a variety
12 of ways to advance. One way, as I mentioned in the opening
13 remarks, would be to see if we can mutually or
14 collaboratively develop some kind of points to consider or
15 guidance so that we are off the same page. That should be
16 shared with the public for input and with the panel for
17 input.

18 You don't necessarily have to do that. You can
19 work off of one or more particular products and you can do
20 that in a pre-IDE, that is, bring protocols to us so that we
21 are working off the same base. We think that a lot of the
22 products you are talking about probably deserve to be IDEs
23 rather than PMAs or 510(K)s because they are in a sort of
24 transitional state and they may for a long time, or maybe
25 forever, be in a transitional state. We have a wide variety

1 of tools and we are quite prepared for, again, either the
2 government or for interested people in the private sector to
3 sit down and try and map out. We have a mandate that is
4 being renewed in the Center to look at least burdensome
5 thresholds. So, that is important to us. Even if it
6 weren't important to us in this particular product line, it
7 is important to us as a general principle.
8 DR. WILSON: Dr. Durack?
9 DR. DURACK: Dr. Gutman, I am actually not quite
10 clear; maybe I just missed something. You might issue a
11 guidance or you will issue a guidance?
12 DR. GUTMAN: Well, it would be our intention to
13 move forward with a guidance or points to consider. Again,
14 I don't want to promise something I can't deliver so we will
15 see how we synthesize everything, and one of the challenges
16 would be whether to try and make some kind of general
17 guidance; whether to try to make some specific guidance
18 after interacting with interested parties if there are
19 particular product lines that seem to be promising or hot;
20 or, frankly, you have already created a guidance to a
21 certain extent in that the transcription for this panel
22 meeting is public and includes the deliberations, and when
23 we interact with any sponsor in the future we will take this
24 as a point to mark in time.
25 DR. DURACK: Thank you. And just for my

1 information, if a guidance did appear what kind of time
2 frame would that likely be?
3 DR. GUTMAN: Well, it takes us month to develop a
4 guidance; hopefully, not years but months.
5 DR. DURACK: Thank you.
6 DR. WILSON: And, Dr. Gutman, is there anything
7 that FDA needs further from the panel?
8 DR. GUTMAN: No, we appreciate your time and
9 attention. Again, I leave the invitation open to interact
10 with us if you have brilliant insights on the plane home.
11 DR. WILSON: All right. If there are no further
12 comments, I would like to thank everyone for coming,
13 particularly our panel discussants, Col. Henchal, Dr. Meyer,
14 and I would also like to thank Dr. Curtis for coming up as
15 well. I would also like to thank the panel members today,
16 particularly those who will not be here tomorrow, Dr. Ng and
17 Dr. Nolte. With that, the meeting is adjourned.
18 [Whereupon, at 3:30 p.m., the proceedings were
19 recessed until Friday, July 28, 2000.]
20 - - -

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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