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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEDICAL DEVICES ADVISORY COMMITTEE

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MICROBIOLOGY DEVICES PANEL

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MEETING
OPEN SESSION

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FRIDAY

OCTOBER 12, 2001

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The panel met in Salons A-C of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, at 9:00 a.m., Dr. Michael L. Wilson, Chairman, presiding.

PRESENT:

MICHAEL L. WILSON, M.D., Chairman

ELLEN JO BARON, Ph.D., Temporary Voting Member

KATHLEEN G. BEAVIS, M.D., Member

KAREN C. CARROLL, M.D., Consultant

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PRESENT (continued):

PATRICIA CHARACHE, M.D., Consultant

FRANKLIN R. COCKERILL III, M.D., Consultant

DAVID T. DURACK, M.D., Ph.D., Industry Representative

JANINE JANOSKY, Ph.D., Consultant

DAVID M. LEWINSOHN, M.D., Ph.D., Guest

VALERIE L. NG, Ph.D., Member

FREDERICK C. NOLTE, Ph.D., Temporary Voting Member

L. BARTH RELLER, M.D., Temporary Voting Member

STANLEY M. REYNOLDS, Consumer Representative

NATALIE L. SANDERS, M.D., M.P.H., M.B.A., Member

FREDDIE M. POOLE, Executive Secretary

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

OPEN SESSION

(9:00 a.m.)

CHAIRMAN WILSON: I'd like everyone to take their seats at this time, please, so we can begin.

Good morning. I'd like to welcome everyone to the meeting of the Microbiology Devices Panel this morning. I'm Dr. Michael Wilson. I'm the Chair of the panel from the University of Colorado and Denver Health Medical Center.

I'd like to begin the meeting this morning by having the panel members introduce themselves. If we could go around, just please state your name and your affiliation. We could start with Dr. Durack.

DR. DURACK: Good morning. I'm David Durack. I'm the industry representative on the panel, and I'm affiliated with Beckon Dickinson and also with Duke University.

MR. REYNOLDS: Good morning. I'm Stanley Reynolds. I'm the consumer representative on the panel. I'm Supervisor of Immunology and Virology for the Pennsylvania State Public Health Laboratory.

DR. CHARACHE: I'm Patricia Charache. I'm affiliated with Johns Hopkins University, a former

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1 panel member, and a consultant for this panel.

2 DR. BARON: I'm Ellen Jo Baron with the
3 Department of Pathology and Medicine at Stanford
4 University, and I am the Director of the Microbiology
5 and Virology Laboratory, Stanford University Medical
6 Center.

7 DR. CARROLL: Good morning. I'm Karen
8 Carroll. I'm Associate Professor of Pathology at the
9 University of Utah School of Medicine and the Director
10 of Microbiology Laboratories at ARUP Labs,
11 Incorporated, in Salt Lake City.

12 DR. SANDERS: Good morning. I'm Natalie
13 Sanders, a general internist with Southern California
14 Permanente Medical Group, also known as Kaiser, and I
15 am on the clinical faculty at the University of
16 Southern California.

17 DR. NG: Good morning. I'm Valerie Ng.
18 I'm Professor and Interim Chair of the Department of
19 Laboratory Medicine at UC-San Francisco. I'm also the
20 Director of the clinical laboratories at San Francisco
21 General Hospital.

22 MS. POOLE: I'm Freddie Poole, the
23 Executive Secretary and Branch Chief for Bacteriology
24 Devices.

25 DR. BEAVIS: Good morning. I'm Kathleen

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1 Beavis, the Director of the Microbiology and Virology
2 Laboratories at Cook County Hospital in Chicago.

3 DR. JANOSKY: Janine Janosky, Associate
4 Professor, Division of Biostatistics, Department of
5 Family Medicine and Clinical Epidemiology, at the
6 University of Pittsburgh.

7 DR. NOLTE: Good morning. Frederick
8 Nolte, Emory University School of Medicine, Department
9 of Pathology and Laboratory Medicine, where I'm
10 Director of the Clinical Micrology and Molecular
11 Diagnostics Lab.

12 DR. RELLER: Barth Reller, Professor of
13 Medicine, Pathology, Division of Infectious Diseases,
14 and Director of Clinical Microbiology, Duke University
15 Medical Center.

16 DR. LEWINSOHN: I'm David Lewinsohn. I'm
17 an Assistant Professor at Oregon Health Sciences
18 University and have a laboratory that's focused on TB
19 T-cell immunology.

20 DR. COCKERILL: I'm Frank Cockerill,
21 Professor and Chair of Microbiology at Mayo Clinic,
22 also Professor of Medicine and Infectious Disease
23 Specialist at Mayo Clinic.

24 DR. GUTMAN: I'm Steve Gutman. I'm
25 Director of the Division of Clinical Laboratory

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1 Devices, FDA.

2 CHAIRMAN WILSON: Thank you.

3 At this time I would like to have Ms.
4 Poole read the conflict-of-interest statements.

5 MS. POOLE: Good morning.

6 The following announcement addresses
7 conflicts-of-interest issues associated with this
8 meeting and is made a part of the record to preclude
9 even the appearance of an impropriety. The conflict-
10 of-interest statute prohibits special government
11 employees from participating in matters that could
12 affect their or their employees' financial interest.
13 To determine if any conflict exists, the agency
14 reviewed the submitted agenda and all financial
15 interests reported by the Committee participants. The
16 agency has no conflicts to report.

17 In the event that the discussions involve
18 any other products or firms not already on the agenda
19 for which an FDA participant has a financial interest,
20 the participant should excuse him or herself from such
21 involvement, and the exclusion will be noted for the
22 record.

23 With respect to all other participants, we
24 ask that in the interest of fairness all persons
25 making statements or presentations disclose any

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1 current or previous financial involvement with any
2 firm whose products they may wish to comment upon.

3 CHAIRMAN WILSON: Thank you.

4 A couple of brief housekeeping items:
5 Please, if you have a cell phone, a pager, or any
6 other device that makes noise, I'd ask you to turn it
7 off during the meeting, so as not to distract the
8 proceedings.

9 The other thing is that, because of the
10 time required to get to the airports now, several
11 panel members reported they have to leave right at or
12 in the middle of the afternoon session. So we're
13 going to try to keep on schedule as much as we can
14 today. Otherwise, we may lose our quorum late in the
15 afternoon.

16 The other thing is, when you come to the
17 microphone to speak, if you could please identify
18 yourself.

19 The item of new business today is a pre-
20 market approval application from Cellestis Limited for
21 the QuantiFERON-TB. This is an in vitro diagnostic
22 device for measuring the release of gamma interferon
23 from sensitized lymphocytes in PPD-stimulated whole
24 blood. This product is intended as an aid in the
25 diagnosis of latent TB infection and to aid in

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1 evaluation of individuals suspected of having M.
2 tuberculosis infection.

3 I would ask all the panel members to hold
4 their questions until after the four presentations by
5 the sponsor. I would like to remind the members of
6 the audience that only the panel can ask questions of
7 the speakers.

8 So at this time I would like to have Dr.
9 Rothel begin.

10 DR. ROTHEL: Hi. I'm Jim Rothel. I am
11 employed by Cellestis Limited as the Chief Scientific
12 Officer and Executive Director, and I own stock in
13 Cellestis Limited.

14 I'd first like to take this opportunity to
15 thank the panel members for coming today, but
16 especially those that had to fly here in these
17 turbulent times. It's not a great experience just at
18 the moment.

19 This first slide is to give you an outline
20 of our presentation today. I'm going to give a brief
21 introduction, and then Professor Tony Catanzaro is
22 going to talk about the current diagnostic methods for
23 TB and limitations of those methods. Then Professor
24 Paul Wood will get up and talk about the scientific
25 basis behind the QuantiFERON technology, and we'll

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1 also talk about the bovine model of the QuantiFERON
2 test. Then I'll come back and talk about the
3 development studies and the clinical studies that
4 we're using to base the PMA submission on.

5 First, this next slide gives us a history
6 of the development of the test. It was initially
7 developed in the mid to late eighties by the
8 Australian Government's research body, CSRO, for the
9 detection of TB in cattle. At that time CSRO got an
10 Australian company called CSL Limited as a commercial
11 partner, and they went on to successfully develop this
12 product into a commercial product which is now sold
13 around the world.

14 Given the success of the bovine test, they
15 then went on to develop a human version of the test,
16 which is called QuantiFERON-TB. There's a large
17 amount of pre-clinical and clinical studies in
18 Australia establishing the test cutoffs and the
19 various parameters of the test.

20 Then the large-scale, pivotal studies that
21 we're using to support our PMA application were
22 conducted by two U.S. Government bodies, the CDC and
23 the Walter Reed Army Institute of Research, which I'll
24 refer to as WRAIR from now on for simplicity. We'll
25 present that later.

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1 I should say the technology is now owned
2 by Cellestis Limited.

3 This slide is a very simple schematic of
4 the methodology of the test. It's simple because the
5 test is simple. How the test is conducted is a
6 heparinized blood sample is collected from individuals
7 and four 1 ml aliquots of blood are pipetted into four
8 different wells of a 24-well culture tray.

9 Then this whole blood -- it's not diluted
10 -- we add the antigens to it. The first antigen is a
11 negative control, which is basically PBS. The second
12 well is tuberculin from *Mycobacterium tuberculosis*,
13 and we'll refer to that as human PPD from now on. The
14 third well is tuberculin from *Mycobacterium avium*, and
15 we'll call that avian PPD. The fourth well is a
16 mitogen-positive control for each individual, and that
17 consists of a submaximal amount of phyto
18 hemagglutinin.

19 Once these antigens are added to the
20 blood, the plate is put in an incubator overnight at
21 37 degrees for 16 to 24 hours. During this period if
22 there are any T-cells present in that blood that
23 respond to mycobacterial antigens -- i.e., if the
24 person has been exposed to mycobacteria -- they're
25 responding in many different ways. But the main one

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1 that we're talking about is the secretion of gamma
2 interferon into the plasma.

3 The next day the red cells are settled
4 down in the 24 wells, and what you simply have is the
5 plasma off the top and then assay for the presence of
6 gamma interferon produced in each of those four plasma
7 samples by a rapid EIA for gamma interferon. We're
8 saying it's rapid. There's only one incubation step
9 where you incubate the plasma and the conjugate at the
10 same time following by a washing step and adding
11 substrate.

12 This slide just depicts the type of test
13 interpretation profile we should get. We'll go into
14 detail a little bit later exactly how the test is
15 interpreted.

16 But an individual who is negative in the
17 QuantiFERON test will not respond to the nil antigen,
18 to the human PPD, or to the avian PPD to any
19 substantial amount and will have a robust response to
20 the mitogen-positive control.

21 A person in whom the test indicates MTG
22 infection will have a strong response to human PPD and
23 also some response to avian PPD, but to a lesser
24 extent. This is due to the cross-reactive nature of
25 the tuberculin antigens in general between the two

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1 species. And, again, a response to mitogen.

2 The person who has reactivity to atypical
3 mycobacteria or mycobacteria other than tuberculosis,
4 or MTRs we'll refer to them throughout the talk, will
5 have the inverse of that response, where the
6 predominant response to the PPD's will be against
7 avian PPD.

8 The mitogen-positive control also serves
9 as a control for the quality of the blood sample to be
10 able to produce gamma interferon or also energy
11 perhaps. An individual in whom a mitogen response is
12 not detectable, a test result cannot be obtained for
13 that individual. That's a very rare event.

14 So I'll just leave you with the intended
15 use and put it upfront. The QuantiFERON test is
16 intended as an aid, and that's an aid in the detection
17 of infection with Mycobacterium tuberculosis.

18 After that brief introduction, I would
19 like to pass it over to Tony Catanzaro to talk about
20 the current diagnostic methods.

21 DR. CATANZARO: Good morning. My name is
22 Tony Catanzaro. I'm with the University of California
23 at San Diego. I've been working on tuberculosis for
24 over 30 years, since my introduction to TB in the TB
25 Branch of CDC. Since then, I have been working with

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1 CDC on a number of projects.

2 One of the projects that I did with CDC
3 recently was to work on QuantiFERON. Because of my
4 work with QuantiFERON, Cellestis asked me to join the
5 Board of Directors, and I'm now a stockholder in the
6 company Cellestis and want to disclose that.

7 But I'm here to talk to you about the
8 clinical aspects of tuberculosis. I want to start by
9 pointing out that the prestigious Institute of
10 Medicine recently published a very important report.
11 In that report they cite that the greatest need in the
12 control of tuberculosis in the United States is a new
13 diagnostic tool to account for individuals who have
14 latent tuberculosis.

15 The reason they focused on that is that
16 CDC has led the charge, and that charge has been
17 joined by the public health community in general,
18 pointing out the way that the identification and
19 treatment of latent tuberculosis infection is the best
20 way to interrupt the transmission of tuberculosis, by
21 preventing active cases from developing from those
22 latent infections.

23 The diagnosis of latent tuberculosis is
24 not a particularly simple task. People have said over
25 and over in talking about this particular test, the

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1 QuantIFERON test, that there's no gold standard, and
2 I'm not exactly convinced of that. It's true there's
3 not a gold standard from a diagnostic or a device
4 point of view, but clinicians are, in fact, able to
5 diagnose latent tuberculosis.

6 They do this by taking into account the
7 history of the patient and the possible exposure of
8 that patient, the epidemiologic status, socioeconomic
9 status, and clinical findings -- all that together
10 with the cell-mediated immune response to
11 tuberculosis. That's what we're talking about here
12 today, one aspect of the diagnosis, specifically, the
13 cell-mediated immune response to tuberculin.

14 That cell-mediated immune response or that
15 TB sensitivity has been measured for 100 years now by
16 the tuberculin skin test, initially developed by
17 Robert Koch and made better by George Comstock and the
18 CDC by a very specific algorithm that's been used.
19 That's the basis that clinicians use to diagnosis
20 tuberculin skin test sensitivity.

21 However, researchers have been very busy
22 for the past couple of decades developing other
23 aspects, other approaches to identifying T-cell
24 reactivity; specifically, lymphocyte proliferation,
25 cytotoxic lymphocyte assays, and the measurement of

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1 cytokine expression.

2 When we look at the tuberculin skin test,
3 I think that the community has done a great job of
4 taking a very old and imprecise technique and really
5 learning how to use it. But I think when we compare
6 the tuberculin skin test with the QuantiFERON-TB, we
7 have to keep in mind the fact that the tuberculin skin
8 test is a very, very complex thing with a lot of
9 little points that a lot of attention has to be paid
10 to.

11 You have to be careful about antigen
12 handling, about antigen deposition in the skin, about
13 reading the tuberculin delay-type hypersensitivity
14 response, which is inherently an inflammatory response
15 locally. It peaks at 48 to 72 hours. The patient has
16 to return for interpretation, and there are almost
17 always reactions to the antigen. That's what it's all
18 about. That reaction is what you read, and
19 occasionally vesiculation and necrosis occur. So
20 there are some adverse effects from that antigen
21 preparation.

22 We've learned to use the tuberculin skin
23 test to a good effect in identifying people who have
24 latent tuberculosis. I think it's important to
25 recognize that there are some shortcomings from a

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1 false negative point of view specifically when we come
2 to the diagnosis of active tuberculosis. Ten to 15
3 percent of cases of active tuberculosis have a
4 negative tuberculin skin test, giving us a sensitivity
5 not of 100 percent, but in fact closer to 50 or 90
6 percent -- in part, because tuberculosis is itself an
7 immunosuppressive disease and in part because of some
8 inherent deficiencies of the tuberculin skin test.

9 Some of those deficiencies revolve around
10 the application. Again, you have to apply it just to
11 the intradermal layer. If it's too deep, the antigen
12 is picked up by blood flow and it's not there 48 hours
13 later for a delayed-type hypersensitivity reaction to
14 occur with.

15 There are also problems with the handling
16 and storage of PPD. Finally, the immune status of the
17 patient, even patients who appear to be immuno-intact,
18 may be immunosuppressed to some extent. All these
19 cause false negative reactions.

20 But the major problems with tuberculin
21 skin tests are in another area. Specifically, the
22 test has to be given and patients need to return for a
23 reading. That's a problem. In many settings --
24 myself, I'm at UCSD Med Center and I run the TB
25 control Lab and I run the skin testing lab. We have

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1 well-trained technicians, highly motivated
2 individuals. About 30 percent of our patients do not
3 return for their reading of the tuberculin skin test.

4 So the antigen is placed. All the costs
5 involved in that are undertaken, but the information
6 is not harvested. That's not a unique experience.
7 That happens in many situations. Patients do not
8 return for tuberculosis skin test reading.

9 Some people say, well, gee, you know, if
10 you're only using it to identify latent TB and they
11 can't come back for the reading, are they going to
12 come back for the treatment? Well, that is a problem,
13 but that's only part of the problem. There's also the
14 epidemiology. There's also understanding how much is
15 tuberculosis a problem in this population. You simply
16 don't know if 30 percent of the readings aren't made.

17 Not to mention the cost implications of not only
18 applying the skin test, but followup and re-followup.

19 These are major problems.

20 There are a number of inaccuracies in the
21 measurement of induration. Measuring the size of a
22 bump in the skin is inherently imprecise. Often we
23 have inexperienced operators. Anybody feels they can
24 read the amount induration, but to read it accurately,
25 to read it within the limits that CDC would like of

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1 plus or minus 2 millimeters is not so easy.

2 But even under the best of circumstances,
3 a 2-millimeter difference is a significant difference.

4 That imparts another problem, which is subjectivity.

5 There's a lot of subjectivity in reading a skin test.

6 This has been demonstrated. There are a number of
7 preferences. Some of these biases are conscious and
8 some of the biases are unconscious and very difficult
9 to control.

10 There are also false positive tuberculin
11 skin tests due to BCG, mycobacteria other than
12 tuberculosis, particularly avium. These are very
13 common in the populations that we're trying to deal
14 with latent TB.

15 The whole southeastern United States has a
16 tremendous problem with hypersensitivity to
17 mycobacteria avium. BCG is very commonly used in many
18 countries from which immigrants come to the United
19 States, and tuberculosis or reactivation of
20 tuberculosis in the immigrant population is a major
21 problem in the U.S. today. At least 50 percent of the
22 new active cases develop in immigrant populations. So
23 this is the target of the latent TB focus and this is
24 a problem for the reading of identification of
25 patients who have latent tuberculosis infection.

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1 I want to talk about the discordance. I'd
2 like to direct your attention to this slide because
3 it's really quite important. We have two products on
4 the market that are approved by the FDA for tuberculin
5 skin test antigens, specifically Tubersol and Aplisol.

6 They were recently studied by Dr. Villarino from the
7 CDC, and a publication in JAMA describes that these
8 two antigens are equivalent and can be used both to
9 measure tuberculin skin test reactivity.

10 But look at the results that were obtained
11 here initially in a low-risk population, 1,555
12 patients. This is with equivalence. We have 10 who
13 had a positive to Aplisol and a positive to
14 tuberculin, and the discordance was 3 and 18 with a
15 Kappa of 0.48. Under most circumstances one would be
16 a little bit concerned about saying that those are
17 equivalent, but in fact they are.

18 The reason they are is because it's
19 recognized by the manufacturers, by the FDA, by the
20 scientific community, that the tuberculin skin test is
21 not a precise measurement. You cannot get 100 percent
22 agreement. This, a Kappa of .48, is considered
23 agreement.

24 The same thing is true in another
25 population of patients with current tuberculosis. The

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1 Kappa there was 0.5. I only point this out to help
2 you understand that, yes, tuberculin skin test is the
3 best we have, but there's a lot of room for
4 improvement there.

5 So I'd like to point out to you the
6 advantages that I, as a clinician, see for the
7 QuantiFERON-TB test. I see us moving from the
8 tuberculin skin test to an objective measurement which
9 is controlled laboratory test, which has a lot of
10 precision built into it and has the opportunity for
11 much better quality control than the whole setup of
12 tuberculin skin test provides for us.

13 It offers the advantage of a single
14 patient contact. We'll be able to get the information
15 as to what the tuberculin skin test reactivity in our
16 population is with one visit.

17 There are no adverse reactions to
18 tuberculin, and this may seem trivial, but in the
19 patients who are reactive to tuberculin they always
20 get pain, discomfort, irritation, whatever.

21 Finally, the test has a built-in control
22 for reactivity to mycobacteria other than
23 tuberculosis, and I think that's a tremendous clinical
24 advantage.

25 So, in conclusion, the tuberculin skin

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1 test is the only currently approved method to identify
2 T-cell reactivity to tuberculin. QuantiFERON-TB
3 solves several important limitations of the tuberculin
4 skin test. QuantiFERON-TB provides an additional tool
5 for clinicians for the identification of T-cell
6 reactivity to tuberculin.

7 Finally, clinicians need to have all the
8 available information to interpret the clinical
9 significance of T-cell reactivity to tuberculin. I
10 want to emphasize that the diagnosis of latent
11 tuberculosis infection is an exercise in clinical
12 medicine, and by definition it requires incorporation
13 of the patient's history, the patient's membership in
14 epidemiologic and socioeconomic status, the physical
15 examination, and an evaluation of tuberculin skin test
16 sensitivity, which can be done classically with a
17 regular skin test and, alternatively, what we're here
18 to talk about today, the QuantiFERON-TB test.

19 Thank you for your attention. I'd like to
20 turn the podium over now to my colleague, Paul Wood,
21 who will talk about the scientific basis of the
22 QuantiFERON-TB test.

23 DR. WOOD: Thank you, Tony.

24 My name is Paul Wood. I was the original
25 inventor of the technology behind QuantiFERON when I

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1 worked for CSRO back in the 1990's. I now work for
2 CSL Limited, and through them I act as a consultant to
3 Cellestis, and I have stock in the company.

4 I want to take you back a bit to when we
5 started. What do we know about mycobacterial
6 infections? Well, one of the things we know is that
7 they induce very strong T-cell responses, one of the
8 distinctions about mycobacterial infections. This is
9 the reason that tuberculin or the tuberculin skin test
10 has been used so many years. We also know that that
11 T-cell reactivity is generated fairly early in
12 infection, and generally maintained for the life of
13 the infection.

14 On the other hand, we know that antibody
15 tends to come up light in infection and it's more
16 mirrored with the mycobacterial load. So when we
17 started off it was obvious for us to look for another
18 measure T-cell-mediated immunity, in this case to look
19 for an in vitro assay.

20 Bovine TB is a very good model for human
21 TB. This is a natural infection, respiratory
22 infection, of an organism in bovis closely related to
23 M. tuberculosis, and, of course, in the early part of
24 the last century, a major infectious disease of
25 humans. The immunoresponse in cattle is very similar

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1 to what we see in human, predominantly a cellular
2 response.

3 Most cattle that we see now, if you class
4 it as having a disease or an infection like LTB, we
5 seldom see generalized TB in animals. The majority of
6 the animals that we detect have single lesions in a
7 lymph node.

8 Similar to what you see in humans, we do
9 see active TB. Often it's in older animals and in
10 undernourished animals. The tuberculin test has also
11 been used in cattle for over 100 years. In this case
12 we use in bovis PPD. It's injected intradermally. In
13 Australia we use the caudal fold.

14 In Europe, in particular, because of the
15 rates of exposure to other mycobacteria, avium is used
16 in comparative tests. So it's comparative testing
17 that's used extensively in Europe. So I contend that
18 we've actually got a very good model for human TB.

19 So why choose interferon gamma as the
20 molecule we're going to measure? One of the tasks we
21 were given is to find a test that you could test 500
22 to 1,000 animals a day. So, obviously, we needed
23 something we use very rapidly. We know, as I said,
24 that TB induces a strong T-cell response. We know
25 that interferon gamma is a classical CMI cytokine.

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1 For those of you familiar with the type I/type II
2 complex of T-cells, you know that interferon gamma is
3 a classical Type I cytokine.

4 We also know it's produced in vitro in
5 response-specific antigens, and it's created in
6 measurable and stable amounts. Very importantly,
7 because we wanted to use whole blood, because, again,
8 as I said, we're looking to test lots of animals in a
9 single day, that it's absent from the normal
10 circulation. There's an extensive literature which is
11 growing all the time showing the importance of
12 interferon gamma in TB infection.

13 The assay in cattle, which we call
14 Govigam, is very similar to what Jim has just
15 described. It uses heparinized whole blood. In this
16 case we substitute bovine PPD for M. tuberculosis PPD.

17 We use avian PPD as a comparator, and we don't use
18 the mitogen. As I said, this was the earlier version
19 and we were testing whole cattle, and you classify TB
20 in cattle on the basis of herd diagnosis.

21 So you incubate overnight, and again if
22 there are specific cells there, they respond and
23 secrete interferon gamma, which we harvest the next
24 day and use a sensitive enzyme immunoassay detect. In
25 this case the monoclonal antibodies are detecting

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1 bovine interferon gamma as distinct from human
2 interferon gamma, as is the case with QuantiFERON.

3 Let me show you some basic raw data. This
4 is the data we generated early, and we got three good
5 animals here. In control animals you see no response
6 or very little response to the PPD's in either of the
7 control, as you can see in the first two animals
8 there. However, with M. avium-infected animals, you
9 see a distinct response to the M. avium PPD. These
10 are just raw OD's I'm showing you here. It's greater
11 than what we see to the bovine response. Of course,
12 if you have M. bovis-infected animals, you see the
13 reverse of that response.

14 As you can see there, this also shows, the
15 point that Jim made, the cross-reactive nature of
16 these antigens in the sense even in the M. bovis
17 animals you can see quite a strong response to the M.
18 avium. That's why we used this comparative. So it's
19 basically an in vitro comparative assay.

20 This is the major study that we did in
21 Australia. So in the study we had over 6,000 animals.

22 All of these animals were tested and eventually
23 slaughtered. The beauty of the cattle model is that
24 we are able to post mortem our animals and collect
25 extensive tissues and culture. So our gold standard

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1 here was M. bovis culture from those animals. In this
2 case we had 125 culture-positive animals.

3 As you can see from that data, the
4 interferon gamma assay was significantly more
5 sensitive than the skin test. The figure there -- we
6 got a 65.6 for the skin test -- was equivalent to
7 studies that Francis did in the seventies, where he
8 came up with a figure of about 70 percent.

9 When we combine the results of the two
10 assays, we slightly increase the sensitivity, but not
11 significantly over and above what we saw with the
12 bovine interferon gamma line. But I point out again
13 that we're able to actually have a gold standard in
14 this trial.

15 More importantly as a scientist, I'm
16 pleased to say that our studies have been consumed my
17 numerous publications. There's over now 20 published
18 studies in 11 different countries. We have 150,000
19 animals that have been tested in those studies. We're
20 coming up with an overall sensitivity of approximately
21 90 percent with a good specificity.

22 What we see in those studies, people have
23 used different cutoffs because people's programs
24 around the world change. So if you're looking for
25 eradication, which is what we did in Australia, then

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1 we maximize sensitivity and we sacrifice a little bit
2 in specificity. In other circumstances where you want
3 high specificity, then you can adjust your cutoffs.
4 But, overall, all of these studies confirm the results
5 we saw in the Australian trials.

6 So what are the lessons we've learned from
7 the bovine assay? Well, in the bovine assay we have
8 found that in general it's more sensitive than skin
9 testing. It's able to detect animals early in the
10 infection. We did in our studies in Brosboteland in
11 New Zealand and also the British now have shown that
12 generally within four weeks of infection -- this is
13 with a low dose, 10-to-the-4 CFU -- you see a positive
14 response. It's maintained for a significant period.
15 We followed animals for three years, and although the
16 actual level varies, they remain positive for all of
17 those three years.

18 It's now used in a variety of countries,
19 including here in the USA. With the white-tail deer
20 problem in Michigan and the spread to cattle, it's now
21 being used in the USA.

22 So, in conclusion, I believe that the
23 whole blood interferon gamma assay is applicable to
24 other mammals. We've now spread it, the technology.
25 We have a primate-based assay that's going through

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1 finalization. We've developed a celine assay we call
2 Cervigam. You see a thing coming through there. And
3 people are now developing it for other species.

4 But, importantly, what you'll hear today
5 is to hear about the human assay. The QuantiFERON
6 assay uses exactly the same technology that I've just
7 gone through in the bovine. It's my belief that the
8 bovine data gives us a good start and extensive
9 validation of the technology.

10 I'll now hand it over to Jim Rothel, who
11 will take you through the clinical data on the
12 QuantiFERON assay.

13 DR. ROTHEL: Thanks, Paul.

14 Tony's gone through the current situation
15 with TB diagnosis, and Paul's just given us a nice
16 overview of the scientific basis of the test in the
17 bovine model. I'm now going to talk about the initial
18 clinical studies that were conducted largely in
19 Australia and then move on to the pivotal studies, the
20 CDC and the WRAIR studies which were using as the
21 basis for a PMA application.

22 A large amount of work was done by CSL in
23 characterizing the performance of the QuantiFERON
24 test, and I'll just go over these points here. The
25 limit of the detection of the test was found to be 1.5

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1 international units of gamma interferon above the nil
2 control for any individual set of plasma samples.
3 That is, a nil for a person, we can detect in a
4 stimulated plasma sample site with a PPD, we can
5 significantly detect 1.5 units above the value in the
6 nil.

7 The linear range of the EIA is on the
8 order of 200 international units per ml. Looking at
9 reproducibility of the test, which is an important
10 aspect, we looked initially at the blood culture
11 phase, the first phase of the test. Looking at
12 replicate cultures, we found the intraclass
13 correlation coefficient to be greater than .95,
14 indicating excellent reproducibility between the blood
15 culture phase.

16 Looking just at the EIA phase, again
17 interferon ELISA, that was found to be highly
18 reproducible as demonstrated by both within-plate and
19 between-plate coefficients of variation being less
20 than 10 percent.

21 Looking at the test overall, looking
22 between blood samples collected and sent to different
23 sites and assayed by different operators, the ICC
24 statistic again was found to be .948, indicating
25 excellent reproducibility.

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1 So after establishing these test
2 parameters, the initial trial we did was that reported
3 by Streeton, et al., in the IITLD journal. This trial
4 was set up to establish the cutoff for the test. We
5 enrolled 407 individuals who were deemed by the
6 ATS/CDC guidelines as being uninfected with TB -- that
7 is class not individuals by those guidelines -- and
8 182 individuals deemed as having latent TB infection
9 by those same guidelines.

10 After testing blood from those individuals
11 in the QuantiFERON assay, we then analyzed the data by
12 ROC curves. This established that the appropriate
13 measure of cutoff is this thing we've called
14 "percentage human response" here, and I'll explain
15 that in a little bit more detail later. We
16 established that should be set at 15 percent. Using
17 this cutoff on that data -- and this data was used to
18 generate the cutoff, but we'll point it out to you
19 anyway -- specificity was found to be 97.6 percent and
20 sensitivity 89.6 percent.

21 We talked earlier about having avian PPD
22 as well as human PPD in the tests, so it's a
23 comparative-type assay. We have to determine the
24 optimal method of distinguishing between TB infection
25 and reactivity to MAC in this case or MOTT, using MAC

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1 as a representative of a MOTT mycobacteria.

2 For this we obtained blood from 50
3 individuals with culture-confirmed TB infection and 10
4 individuals with culture-confirmed MAC lymphadenitis.

5 This graph there on the bottom, which is hard to see
6 no doubt, but you can get the feeling, up the side
7 here is the second cutoff we've chosen -- I hope I
8 don't zap you with this laser pointer over there -- is
9 the percent avian difference, which is the second
10 cutoff we've chosen. Again, I'll explain it in a
11 minute.

12 These individuals here are TB patients.
13 These are the patients with MAC infection. The line
14 across there, which is set at minus 10 percent, was
15 chosen as the optimal cutoff to discriminate between
16 those with TB infections and those with reactivity to
17 MOTT.

18 So just to go through how those two
19 cutoffs are chosen, the percentage human response is
20 the response of an individual to human PPD expressed
21 as a percentage of their response to the mitogen
22 control well. These values are both corrected for
23 nil.

24 The percent avian difference is calculated
25 by subtracting the response to avian PPD from that to

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1 human PPD and expressing that as a percentage of the
2 response to human PPD, again corrected for nil. That
3 sounds a little complicated, but it's a very simple
4 calculation. But what that essentially says is, what
5 is the predominant response to? Is it to human PPD or
6 to avian PPD?

7 One other or two other factors have to be
8 included in the cutoffs used for the tests. As I told
9 you earlier, the limit of sensitivity for the
10 QuantiFERON EIA is 1.5 units per ml. So, therefore,
11 to obtain a valid test result for any individual,
12 their mitogen response has to be at least 1.5
13 international units above the nil sample for that
14 individual. If it's not, that's an invalid test and
15 we can't obtain a test result for that person. Again,
16 that's a rare event. Similarly, seeing the
17 sensitivity of the EIA is 1.5 units above nil, the
18 human PPD minus nil has to be greater than that level
19 to obtain a positive response in TB.

20 So now that we have established these
21 cutoffs, we went ahead and did some clinical trials,
22 some more clinical trials. What we would have loved
23 to have done is to look at the response of individuals
24 before being infected with M. tuberculosis and then
25 following MTB infection, but ethically that's a very

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1 difficult experiment to do. So we did the next best
2 thing and used an MTB complex organism, albeit very
3 attenuative, which is in bovis BCG.

4 We recruited 53 low-risk TB individuals,
5 that being medical students in Australia who are
6 routinely BCG vaccinated, at this university at least,
7 and tested them with QuantiFERON both before BCG
8 vaccination and then five months after BCG
9 vaccination. The data showed that 92 percent of these
10 medical students showed an increase in their
11 QuantiFERON response after BCG vaccination, and the
12 amount of this increase was threefold above that found
13 prior to BCG. I should add here that the vast
14 majority of these were still below the 15 percent
15 cutoff that was established for the QuantiFERON-TB
16 assay, but that would be expected, knowing the BCG is
17 a highly attenuated MTB complex organism.

18 First, we feel that this study
19 demonstrates that an increase in QuantiFERON-TB
20 response is generated following MTB infection. We
21 have now established from the Streeton study and from
22 these other studies that the majority of people who
23 are not infected with TB don't respond in their
24 QuantiFERON-TB test, and the majority of people that
25 have latent TB infection give a positive response in

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1 QuantiFERON-TB. But what about those with active TB
2 disease?

3 To look at this, we conducted a multi-
4 center study in Australia, nine different hospitals
5 around Australia, and recruited 129 individuals with
6 culture-confirmed TB disease. Eighty-one percent of
7 these patients were found to be QuantiFERON-positive,
8 and this established that the test works in cases of
9 active TB disease, where commonly the immune response
10 is quite depressed to tuberculin.

11 That's a brief outline of the clinical
12 studies that were conducted in Australia. Let's move
13 on to the pivotal studies that were conducted by the
14 CDC and Walter Reed.

15 First, I want to talk about the
16 constraints of running clinical trials of any test for
17 latent TB infection. There's no gold standard for
18 latent TB. Tony told us about it before, and there
19 just isn't a standard for it. Now TST is an aid to
20 detecting tuberculosis infection. As Tony eloquently
21 put, it's not a gold standard. It's definitely not a
22 definitive indicator for LTB. So, therefore, we
23 didn't have a gold standard. What do we do?

24 So the data analysis method we used was to
25 recruit individuals with no known risk factors for TB

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1 infection and then use these to determine what are
2 termed apparent specificity. We called it apparent
3 specificity because we cannot guarantee that some of
4 those individuals did not have latent TB infection,
5 although the chance of that is very low.

6 To determine the sensitivity of the test
7 for active TB disease, we do have a gold standard.
8 It's culture of the organism. So for that, we can
9 recruit culture-confirmed TB cases.

10 But the last group there on that slide is
11 looking at the sensitivity of the test for latent TB
12 infection. Without a gold standard, all we can do is
13 recruit individuals with identified risk factors for
14 latent TB infection and look at the concordance with
15 this suboptimal standard TST. That's the best
16 available to us.

17 So the CDC study recruited 1,500 subjects,
18 or that was the goal. There were five different sites
19 across the U.S., which was San Francisco, San Diego,
20 Baltimore, Newark, and Boston. The main aim was to
21 look for a concordance between QuantiFERON and the
22 TST.

23 The four groups enrolled: a low-risk
24 group, 98 individuals, and that was to look for
25 specificity of the test; a medium to high-risk group

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1 that included contacts of active TB cases, immigrants
2 from high-risk countries, homeless people, et cetera;
3 TB suspects, people suspected of having active TB
4 disease. And these three groups represent the
5 intended population for QuantiFERON TB.

6 The fourth group that was included in the
7 CDC study were those individuals that had culture-
8 confirmed TB in the past and had completed their
9 therapy for that within the previous two years.
10 They're not in the intended population. For many
11 reasons, they are not appropriate for us to study and
12 we are not presenting any data from those.

13 For the Walter Reed study, there was
14 nearly 1,700 recruits at the Great Lakes Navy Station
15 in Illinois. These were stratified into three groups,
16 the first group being 397 individuals with no
17 identified risk factors for TB.

18 The second group had one limited risk
19 factor, which is they were born in or recruited into
20 the Navy from a U.S. state that had a TB rate of 10
21 per 100,000 or greater. This is a very low risk
22 factor, I'll acknowledge that. What we were trying to
23 do here was to make group one as TB risk-factor-free
24 as we possibly could, but I'll acknowledge that group
25 two is a very low respecter as well.

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1 Group three individuals were those who had
2 identified respecters. The majority of them were born
3 overseas, although there were some recruits that
4 reported contact with active TB in the past.

5 Adverse events, there were no adverse
6 events reported in the CDC study for the
7 QuantiFERON-TB, where there was 9.4 percent of
8 individuals in the CDC study reported an adverse event
9 for the TST.

10 Looking at the sensitivity first of
11 QuantiFERON-TB for active TB disease, there were 94
12 people enrolled into the CDC study group three.
13 They're the TB suspects group. After culture was
14 performed, 54 of these were found to be MTB culture-
15 positive. Forty-four of these, or 81.5 percent, were
16 QuantiFERON-TB-positive, indicating that the
17 sensitivity for QuantiFERON-TB, using that trial 15
18 percent cutoff we had established, was 81.5 percent.

19 Now this has to be the minimum sensitivity
20 of the test for latent TB as well, because it's well
21 acknowledged in the scientific literature that people
22 with culture-confirmed TB disease often have depressed
23 cellular immune responses, including gamma interferon
24 responses.

25 We now look at the apparent specificity of

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1 QuantiferON-TB, look at the three low-risk groups, one
2 from the CDC and two from the WRAIR study. Using the
3 TST at 10 millimeters and the QuantiferON at a trial
4 cutoff of 15 percent, we found the specificity of the
5 TST 95.9 in the WRAIR study compared to 91.8, 98.7,
6 95.5 for the WRAIR low-risk group and 98 compared to
7 93.4 for the limited-risk.

8 But these individuals, group one
9 individuals, are not recommended by the CDC ATS
10 guidelines to be screened for TB. In reality, they
11 are. The military is a prime example of an
12 institution that routinely screens individuals with no
13 risk factors. So it's important to be able to have a
14 test that works for them.

15 For the TST, a stratified cutoff of 15
16 millimeters is used for these individuals. We can do
17 exactly the same thing with the QuantiferON test, and
18 we have established that a 30 percent cutoff is the
19 optimal cutoff to use in individuals like this with no
20 identified risk factors.

21 So if we look now at the specificities for
22 these three groups, three study groups, using the TST
23 at the stratified 15 millimeters or QuantiferON at a
24 proposed 30 percent stratified cutoff for such
25 individuals, you can see that the specificities in

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1 general are 98 percent.

2 Now we're looking at individuals at risk
3 of being infected with latent TB. This is a two-by-
4 two table obviously comparing QuantiFERON with TST.
5 We're looking here at individuals from the CDC study
6 recruited into group one or group two. That's low-
7 risk or high-risk.

8 For the TST we're using a risk-stratified
9 cutoff where the individuals in group one, we use a
10 15-millimeter cutoff for the TST, and for group two we
11 use a 10-millimeter cutoff. This is comparing
12 QuantiFERON-TB to the trial cutoff of 15 percent.

13 You can see that concordance is quite good
14 with 85 percent of the individuals having concordant
15 results with the TST, although there are a significant
16 number of individuals that have discordant results on
17 both sides of the diagonal. Kappa here was .554,
18 indicating moderate, verging on good, agreement.

19 But if we use a stratified cutoff that
20 we're proposed for group one individuals, what happens
21 to the data? For groups one's, we use the 30 percent
22 human response cutoff for QuantiFERON and 15
23 millimeter for TST, and group two we use 15 percent
24 cutoff that was established in the Australian trials
25 and a 10-millimeter cutoff for the TST.

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1 We find that the sensitivity of the test
2 is maintained. The only people that have moved in
3 that two-by-two table are those individuals that were
4 in group one, the low respecters, and we're assumed
5 that they're all negative, that they don't have TB
6 infection.

7 Kappa for this was .561, again indicating
8 moderate to good agreement. I would point out again
9 that this is a similar, slightly better Kappa than
10 that attained when comparing Aplisol to Tubersol both
11 in low-risk and TB-infected individuals.

12 So what are the potential reasons for the
13 discordance we've just seen? It was random variation
14 as you'd expect to see; again, as the Tubersol versus
15 Aplisol story. If we look at the individuals that
16 were positive in the TST but negative in the
17 QuantiFERON test, 13 out of 80 of them demonstrated
18 MOTT reactivity by the QuantiFERON test, and MOTT is a
19 well-known source, MOTT reactivity is a well-known
20 source of false positive TST reactions.

21 There was a significant association with
22 individuals being BCG-vaccinated having that same
23 response, being TST-positive, QuantiFERON-negative,
24 suggesting that perhaps the TST is more affected by
25 BCG vaccination than is QuantiFERON-TB.

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1 Two other factors were found, age and
2 gender, and we really don't have any explanation for
3 why they should be associated with discordance.

4 So now we've shown that QuantiFERON-TB
5 detects M. tuberculosis-specific T-cell responses.
6 We've demonstrated with people that don't have TB
7 infection the vast majority are negative in the test,
8 98 percent of them. We've shown that individuals that
9 definitely have TB disease, as demonstrated by
10 culture, 81.5 percent were found to be positive. And
11 we've demonstrated good concordance with the TST at 85
12 percent in those at risk of LTBI.

13 But although we can explain some of the
14 discordant results found by MOTT reactivity, as
15 demonstrated by QuantiFERON in those TST-positive,
16 what's the best way of demonstrating this? It's
17 looking back, I believe, at the extensive data from
18 the bovine animal model, which is an excellent model
19 for TB for humans.

20 This slide shows two-by-two tables. The
21 top table here is the data that you've seen before for
22 the CDC group one and two individuals combined. The
23 data down below is a study from the Wood, et al.,
24 paper, the key publication that Paul Wood referred to
25 earlier with 86,000 cattle tested.

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1 What I want you to focus on here are the
2 numbers, the percentages in brackets. These
3 percentage values are the percentage of individuals,
4 or in this case individuals, who are positive to one
5 or both of the tests. So 48 percent of individuals
6 were positive to both of the tests as compared to
7 positive to any.

8 The same thing down here for the animals,
9 the cattle in that study. You'll see there very
10 strong similarity between the percentages of
11 discordant values found between the human test and the
12 bovine test. So the same level of discordance is
13 found in the bovine assay.

14 But the big thing about the bovine test is
15 that we could kill the animals, we could take out
16 extensive tissues out of these animals, slaughter them
17 in the laboratory, and culture for M. tuberculosis
18 disease, looking for foci of infection.

19 If you now look at the data based on
20 culture, stratified by positive culture, you'll see
21 that the animals that were positive to both tests, the
22 TST and the bovine equivalent of QuantiFERON, 87
23 percent of those doubly positive were found to be
24 culture-positive. But for those that were positive
25 just in the TST and negative by the QuantiFERON or the

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1 bovine version of it, 53 of them, only two of them
2 were found to be culture-positive. So 4 percent.

3 So the sensitivity of the TST, when it was
4 positive only by itself, it was very low. Conversely,
5 if we look at the animals that were positive by the
6 bovine gamma interferon assay and negative in the TST,
7 55 percent of them were found to be culture-positive.

8 Paul showed you these figures before, but
9 the TST sensitivity from this study was 65.6 and for
10 the gamma interferon assay it was 93.6 percent. So
11 it's reasonable to assume, to extrapolate from this
12 bovine model, that for discordance results in the
13 human test it's reasonable to suggest that those gamma
14 interferon-positive are more likely to be truly TB-
15 infected.

16 Just to go through the conclusions, Tony
17 told us there definitely is a medical need for an
18 improved diagnostic test for latent TB, as indicated
19 by the IoM report that came out last year. Paul told
20 us about technology, and it's based on sound, very
21 well-established scientific principles. Hopefully,
22 I've just shown to you that QuantiFERON is a very
23 sensitive test and highly specific for the protection
24 of TB infection.

25 QuantiFERON has a major logistic advantage

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1 over TST, and that is people don't have to come back
2 to get a result. As Tony told you, 30 percent, or in
3 many cases many more than 30 percent, of individuals
4 you don't get a result when using the TST. With the
5 QuantiFERON test, you will get a result close to 100
6 percent of people.

7 QuantiFERON is a controlled, laboratory-
8 based test. It's not subject to those subjective
9 issues that TST is well-known for. It accounts for
10 activity in the MOTT, and the initial data says that
11 it appears to be less affected by BCG than is the TST.

12 I'd just like to conclude by showing this
13 slide. We believe the data provide reasonable
14 assurance of the safety and efficacy of QuantiFERON-TB
15 as an aid in the detection of infection with
16 mycobacterium tuberculosis.

17 Thank you for your attention.

18 CHAIRMAN WILSON: Thank you.

19 At this time I would like to invite the
20 panel members to begin asking questions. Dr. Durack?

21 DR. DURACK: Several short questions for
22 Dr. Rothel. If this test becomes widely used, which
23 I'm sure you'd be pleased to see, what is the story
24 about the supply of mitogens? Is it adequate,
25 reliable, quality-controlled, and would there be

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1 enough for an extensive application of this test?

2 DR. ROTHEL: Yes, the mitogen is a
3 commercial product that I bought from Streeton -- I'm
4 just trying to think who -- but it's commercially
5 available and there's no problem with supply of it.

6 DR. DURACK: Standardized and
7 reproducible?

8 DR. ROTHEL: Standardized and it's
9 standardized in-house as well.

10 DR. DURACK: A question about the nil
11 response: Do you see much variation in the nil
12 response? What's the range?

13 DR. ROTHEL: The general range of the nil
14 response would be from an optical density, if we talk
15 optical densities, from zero to about .07.

16 DR. DURACK: Okay.

17 DR. ROTHEL: Occasionally, you do get an
18 individual that has a higher response in the nil, and
19 this is due to competing factors such as heterophile
20 antibodies that are common when you're using an ELISA
21 that uses unique plasma samples. The assay, again
22 interferon EIA, is heavily formatted to reduce it for
23 all antibody activity, but occasionally perhaps some
24 person has very high reactivity there and we don't
25 compute it all out. But, again, it doesn't affect the

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1 result of the test because that variable is subtracted
2 from all the other plasma sample wells.

3 DR. DURACK: A question regarding the
4 human versus the avian test: How often do you see an
5 equivocal response, if you like, where they're about
6 equal? Would you comment on that? Does it happen?
7 How would you interpret it?

8 DR. ROTHEL: The cutoff has been fairly
9 extensively backed up by the data we've seen, I must
10 say. In the vast majority of cases -- and this is all
11 off-the-top-of-my-head stuff without having the data
12 in front of me to show you -- but in the vast majority
13 of cases a person who is infected with TB, such as a
14 culturally-confirmed TB case, the response to human
15 PPD I would guess would be at least twice that to
16 avian PPD, and the inverse in the few individuals who
17 are seen that have had MAC infection.

18 DR. DURACK: Have you seen examples where
19 the response is about equal?

20 DR. ROTHEL: Off the top of my head, I'm
21 sure we have, but I can't come up because I don't
22 really know any of them. I can't think of any
23 specific examples.

24 DR. DURACK: Right. One last question:
25 You've touched I think several times on this, but the

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1 degree of the response, the quantitative response, can
2 you comment on the correlation between active disease
3 versus latent disease and the correlation coefficient?

4 DR. ROTHEL: Yes, quite often people with
5 active TB disease you get very low responses within
6 the sensitivity of the test to both mitogen and to the
7 human PPD, but they still come out positive, whereas,
8 typically, individuals who would be suspected of
9 having latent TB infection, the responses are much
10 more robust.

11 DR. DURACK: Thank you.

12 CHAIRMAN WILSON: Dr. Cockerill?

13 DR. COCKERILL: Yes, a couple of
14 questions. I know that the datasets are limited, but
15 in the studies you've done and in the studies
16 reported, is there any information regarding the test
17 when applied to children?

18 DR. ROTHEL: We've excluded, limited our
19 tests to not cover children, but, yes, there is a
20 large body of data available in Australia from
21 specifically one physician, Jonathan Streeton, that
22 original paper, who has been using the test for many
23 years. He routinely uses it in children in contact
24 situations, and that has got excellent results. But
25 we realize we have to do studies in children to be

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1 able to gain approval for use in that population.

2 DR. COCKERILL: And among the patients you
3 studied or other studies that have been done, patients
4 who were leukopenic, any information regarding the
5 validity of the testing in those patients?

6 DR. ROTHEL: Again, excluded from there,
7 labeled on things, but, yes, we have done studies in
8 HIV-infected individuals both in Kenya -- and I think
9 there was attached to your panel packet a summary of
10 that study. Also, some studies have been initiated in
11 Australia looking at the response to mitogen relative
12 to CD-4 counts in HIV patients.

13 It's actually quite surprising; quite a
14 number of individuals with CD-4 counts less than 50
15 give quite strong responses to the mitogen still.
16 Then, again, others don't. But generally, if they're
17 over 200 CD counts, 200 per ml., they do have a
18 measurable response. Less than that, it gets a bit
19 equivocal.

20 CHAIRMAN WILSON: Dr. Reller?

21 DR. RELER: Dr. Wood, in the schema you
22 used blood collected in tubes with heparin. What
23 about other anticoagulants and the effect on the test:
24 EDTA, citrate, SBS, et cetera?

25 DR. RADFORD: Yes, we tried sodium

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1 citrate, one or two other anticoagulants. None of
2 them actually work. When you look at it, because
3 we're using whole blood, they actually interfere with
4 the interaction between the antigen-presenting cell
5 and the T-cell. So heparin is the only anticoagulant
6 that will work in the system.

7 DR. ROTHEL: That's also been validated in
8 the human assay.

9 CHAIRMAN WILSON: Dr. Charache?

10 DR. CHARACHE: I didn't tell you what I do
11 at Hopkins, but I am an infectious disease consultant
12 as well as a microbiologist, and I'm telling you this
13 to give you my orientation, which is to say that I
14 very strongly agree with the advantages of a
15 laboratory test as opposed to a skin test.

16 I do see some very basic questions here in
17 its current formulation, not what else may we do, but
18 I think perhaps I can show it best if we look at the
19 concordance. I was, as an example, looking at the
20 concordance in the WRAIR study of all tests. In our
21 book it's on page 77.

22 Now the WRAIR group does not match the TB
23 population that we usually look at, which is much more
24 diverse in terms of age and underlying pathology, but
25 it has the advantage of being young, Navy recruits, so

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1 it can get a good look at the lower-risk group. If
2 we look at all comers in the WRAIR group, looking at
3 the positives, because to me it's the positives that
4 are important, not the negatives, because we're
5 looking for latent disease, there are 18 in which
6 there's concordance. There's 105 in which the
7 QuantiFERON is positive and the latent is not. So,
8 clearly, they're measuring different things. There's
9 a tenfold difference.

10 We do know that this group includes the
11 low-risk which has a high percent false positives on
12 the tuberculin test, meaning that many of the 18 that
13 were in the low-risk population are false positives.
14 That raises the very serious question about the false
15 positives with this test.

16 If we look on the next page at the low-
17 risk group using the 10-millimeter cutoff -- I think
18 it's two pages -- the moderate-risk category, primary-
19 risk individuals, we similarly see a skewing, not
20 quite as bad in this one, but you end up with a 15.1
21 percent positive rate for the QuantiFERON. Now if we
22 translate that 15 percent into positive per 100,000,
23 which is the way it's expressed generally, that group
24 should have 10 patients or 10 subjects per 100,000
25 individuals which is positive. If this test were

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1 correct, it would come out to something like 15,000
2 patients per 100,000 positive.

3 And the same is true as you look at the
4 others. The number that would be called positive, if
5 we use this particular test, particularly in the low-
6 risk population, would be between -- well, in the CDC
7 study it would be 8,300 per 100,000. That's way out
8 of line with what all the epidemiologic studies have
9 said it should be. And your slide used the number 10
10 per 100,000 for your category two. This comes out,
11 when you add the zeroes, to 15,000.

12 So I think it's going to be very important
13 that we understand why this is calling so many more
14 people positive or we're going to have a very abrupt
15 jump in our incidence of tuberculosis in the United
16 States that we're going to have to explain.

17 DR. ROTHEL: Sure. Can I reply to the
18 last bit first, get that out of the way? The 10 per
19 100,000 is the rate for active TB cases per 100,000
20 individuals. We're looking at latent TB infection,
21 which is meant to be at least 10 to 100 times higher
22 than that for active TB cases.

23 Did I understand your question wrong? Is
24 it that --

25 DR. CHARACHE: Actually, the numbers don't

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1 come out quite like that from the literature which I
2 saw.

3 DR. ROTHEL: Yes.

4 DR. CHARACHE: But, in any event, what
5 we're seeing is that for those at lower risk the
6 QuantiFERON has eight to ten times the number of
7 positives as the skin test does.

8 DR. ROTHEL: Sure, sure.

9 DR. CHARACHE: And then we know that it's
10 not as sensitive as the skin test when we get to the
11 active TB model, where it's less sensitive. So I'm
12 questioning what this problem is that we're seeing
13 with the discrepancies between these tests that is so
14 striking and how do we adjust for them.

15 I'm interested in knowing what your
16 discordance effects of age and gender are, and in the
17 CDC study they noted there was discordance differences
18 in results according to the particular study site that
19 did the evaluation, in their table, that it mattered
20 whether you were in site E or site A in terms of
21 results. So I'm wondering if you can help us
22 understand some of the factors that we then could
23 modify or adjust, as you have considered adjusting
24 your criteria for the lower-risks, and so on.

25 DR. ROTHEL: There's a lot of questions in

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1 what you have just asked me. I hope I can remember to
2 answer them all.

3 The first one, if we go back in order, as
4 far as the sensitivity in the low-risk WRAIR
5 individuals, we're proposing to use a 30 percent
6 cutoff in those individuals. We're not proposing to
7 use the 15 percent cutoff. That large number you're
8 talking about of individuals positive in
9 QuantiFERON/negative in TST largely disappears if we
10 use a 30 percent cutoff.

11 What we can assume in those individuals is
12 none of them are truly infected. That's the
13 assumption we make, and that was the basis of the
14 study. So a similar number of falsely positive by TST
15 is falsely positive by QFT, would be my response to
16 that.

17 DR. CHARACHE: Now wouldn't that same
18 propensity for false positives perhaps be carried over
19 into the other populations? They're just hidden?

20 DR. ROTHEL: Sure, sure, and there's
21 wobble in any biological test like this. That's the
22 range of variables I was talking about in my
23 presentation. We're always going to get false
24 positives in any test. It's the nature of biological
25 tests.

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1 Now where were we?

2 DR. RADFORD: I think Tony's actually got
3 a comment to make to this topic. So I would just ask
4 him to speak.

5 DR. CATANZARO: I just wanted to talk
6 about the purpose of screening in the Navy, for
7 example. Obviously, you and I are both clinicians,
8 and we're interested in patients with disease. But in
9 that setting the purpose is actually to find
10 individuals who are completely free of any suspicion
11 of disease.

12 So the fact that a large number of Navy
13 recruits were correctly identified as being free of
14 tuberculin sensitivity is the object of the exercise.

15 Now I grant you that this presents more workload to
16 the clinician to look at these people who are reactors
17 to tuberculin and figure out whether that reactivity
18 is due to tuberculosis disease or due to some other
19 immunologic phenomenon.

20 But I think as a public health person, and
21 particularly as someone who's going to put young men
22 on a Navy submarine, for example, the fact that you've
23 identified a huge number of individuals who are
24 clearly free of tuberculin reactivity is the purpose
25 of the exercise.

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1 DR. CHARACHE: I'm concerned about how
2 it's going to be used and the toxicity of the drugs
3 that will be applied, if we have false positives. So
4 I'd like to see if we can't get rid of some of them.

5 DR. CATANZARO: I think you're absolutely
6 right. That was the purpose of my presentation saying
7 that a positive reaction to tuberculin skin test or,
8 for that matter, to QuantiFERON does not result
9 necessarily in the application of therapy. There's a
10 clinician between the two who plays a very important
11 role. There are many people who have tuberculin
12 sensitivity with the tuberculin skin test who are not
13 candidates for INH prophylaxis, and the same will be
14 true for QuantiFERON.

15 DR. CHARACHE: If you have a positive
16 QuantiFERON, knowing that there may be a very high
17 false positive rate, based on the low-risk group where
18 we can perhaps see it best, what would you tell the
19 doctor to do to prove there was or wasn't latent TB?
20 Would you suggest they do a skin test or --

21 DR. CATANZARO: No.

22 DR. CHARACHE: -- how else would you
23 decide whether to use antibiotics or not?

24 DR. CATANZARO: No. First of all, we
25 propose the gradation of having a 15 percent cutoff

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1 and a 30 percent cutoff. This is analogous to what we
2 do with the tuberculin skin test: a 10-millimeter
3 cutoff in certain situations, a 15-millimeter cutoff
4 in other situations.

5 But what I would recommend to that
6 individual, just like I do with tuberculin skin test
7 reactivity -- and I've been doing this for the past 30
8 years, and you have as well -- you see an individual
9 who's got a 10-millimeter tuberculin reaction. You
10 get a history.

11 If that person has, for example, been
12 brought up in Peru and been given BCG three times as
13 he was growing up and now is 25 years old, it's likely
14 that that 10-millimeter reaction was due to BCG. If
15 that individual was raised in Atlanta in a low
16 socioeconomic -- excuse me -- was raised in Atlanta,
17 had a 10-millimeter reaction, chances are that it well
18 be avium. On the other hand, if that person was
19 raised in California, the son of a mother with active
20 tuberculosis when he was 10 years old, that 10-
21 millimeter reaction is most likely due to
22 tuberculosis.

23 So you have to apply, I think, clinical
24 judgment to the tuberculin reactivity with tuberculin
25 skin tests and the same is required by QuantiFERON. I

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1 do think that there are a large number of false
2 positives. I think that this wobble effect of getting
3 a different reaction to QuantiFERON than you do with
4 tuberculin skin test is exactly the same as we see
5 with the tuberculin using Tubercol versus Aplisol. I
6 don't think you'd identify one of those as false
7 positives, just different.

8 DR. CHARACHE: Well, yes, I think that
9 obviously suggests that the product has different
10 antigenic properties in terms of stimulating your
11 immunity. Here we have a very different mechanism.
12 I'm satisfied, I think, as all of us are, that if we
13 have a simple test that can be done effectively to
14 screen for experience with the mycobacterium
15 tuberculosis, it would be used very widely. I
16 certainly favor this.

17 I'm questioning how to make it more
18 precise, because when we do the math in its current
19 form, we would have statistics that are quite
20 disparate from past experience.

21 DR. CATANZARO: I want to make one more
22 comment, if I may, regarding the question you asked,
23 "Would you do a tuberculin skin test?" I would no
24 more do a tuberculin skin test for a questionable
25 QuantiFERON than I would do a Coghnaunt skin test with

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1 a questionable Aplisol. I think that to do that is
2 trying to beat a technology beyond its capabilities.

3 The disparity between Aplisol and
4 Coghnaunt tuberculin skin test reactivity is not due
5 to measuring very different things. It's due to the
6 inherent error in the biological assessment of
7 tuberculin skin test reactivity. You have to go to a
8 completely different system; for example: history,
9 physical exam, et cetera. That's my point of view
10 anyway.

11 DR. CHARACHE: Well, I would think it
12 might be helpful to see if we can understand better
13 some of these discrepancies and what it looks like
14 when you use 30 in the most unlikely to have TB. We
15 haven't seen that data. But, also, when we look at
16 the higher groups, we can still see things that we
17 really can't explain too easily.

18 There was one comment that there were 55
19 patients tested who had discrepant TD skin test
20 compared to the QuantiFERON, and there were 39 that
21 were retested. Of those 39 that were retested, only
22 18 were repeat positive with the QuantiFERON. So I
23 think these are some of the questions I have in terms
24 of how we can improve it.

25 DR. ROTHEL: Introduce yourself.

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1 DR. RADFORD: My name's Tony Radford. I'm
2 the Chief Executive Officer of Cellestis, and I also
3 have a shareholding in the company.

4 I think that I could perhaps best address
5 your question by putting up an overhead which looks at
6 the percentage positive in all of the studies that
7 we've done, all the risk groups from one, two, three
8 and all the Walter Reed studies, using the risk-
9 adjusted cutoff at 30 percent for low-risk or what you
10 might call almost no risk groups. I think if you look
11 at the percentage figures there, you will see that the
12 percentage differences are really quite small and
13 won't lead to major changes in epidemiological beliefs
14 in the instance of tuberculosis. That slide's just
15 going up behind you.

16 You'll see that it's the Walter Reed low-
17 risk group on the left, again, using risk-stratified
18 cutoff both for QFT and the tuberculin skin test.
19 What you can see is that the percentages very closely
20 parallel each other in each of the independent groups.

21 We come up here to, of course, the top.
22 This is the active TB group. You come down here to
23 the at-risk group, and if I go to the Walter Reed
24 primary risk group, what you'll see in that primary
25 risk group, where there is a higher risk of

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1 tuberculosis and it is, in fact, a reasonable
2 percentage, they are closely parallel. As we go
3 across into our lower-risk groups, we're applying
4 stratified cutoffs in both cases, and you will see
5 there is no significant change to the instance of
6 tuberculosis.

7 So I don't think you'll find there is a
8 major change in the epidemiological beliefs in the
9 country in the incidence of latent tuberculosis using
10 this test.

11 DR. CHARACHE: Okay, I'm working from the
12 tables in which there are three risk groups rather
13 than six. So I couldn't really relate to this.

14 DR. ROTHEL: The data I think that you
15 want to see is what I've presented in the talk. On
16 the second one of those specificity slides -- I think
17 you have a copy of the slides -- where we apply the
18 15-millimeter cutoff to the TST and the 30 percent
19 cutoff for QuantiFERON. I think they're the figures
20 you're wanting to see. Am I correct?

21 DR. CHARACHE: I'm sure you have it.

22 DR. ROTHEL: Oh, we do have it, yes. We
23 can put it up.

24 CHAIRMAN WILSON: Dr. Janosky.

25 DR. JANOSKY: Just a very quick followup

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1 to the question that was asked: Do you have the data
2 to show us the discordance based on age and gender?

3 DR. ROTHEL: Yes.

4 DR. JANOSKY: What's the directionality of
5 the discordance of what I'm actually looking --

6 DR. ROTHEL: Yes, I can talk to it; it is
7 probably easiest. The table that was in your panel
8 pack actually shows the moderate directional analysis
9 legacy regression.

10 Age was associated with a positive
11 TST/negative QuantiFERON. Age greater than 60 was
12 associated with that type of discordance. Male sex
13 was associated with having a positive
14 QuantiFERON/negative TST.

15 DR. JANOSKY: I did see it in the panel
16 packet, but just to refresh my memory again, you're
17 saying males are more likely to be called positive
18 when they're not and older individuals are more
19 likely?

20 DR. ROTHEL: Males are more likely to have
21 a QuantiFERON positive/TST negative response than
22 having a concordant response with both tests, either
23 doubly positive or doubly negative. So that was the
24 reference group for all of that discordance analysis
25 for individuals with concordance results.

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1 DR. JANOSKY: Okay. That's what I needed.
2 Thank you.

3 CHAIRMAN WILSON: Dr. Lewinsohn?

4 DR. LEWINSOHN: I guess a couple of
5 questions. The first was I think a test that doesn't
6 require coming back to the doctor obviously has some
7 real advantages over the current skin test. So I was
8 just looking over the data that's on page 40 that had
9 to do with exclusions from the trial. I'm just trying
10 to add these up very quickly, but it looked as if
11 about 70 were excluded because of reasons sort of
12 related to the QuantiFERON test; that is, unable to
13 draw blood, insufficient blood, blood clotted, or
14 other QuantiFERON errors, and about 130 were excluded
15 because of TST errors.

16 I guess my question was, and this is in
17 the context of a clinical trial where things are being
18 done very carefully: What's been your experience with
19 regard to blood being drawn for the QuantiFERON and
20 then ultimately not actually having the test
21 successfully done?

22 DR. ROTHEL: It's a fairly uncommon event,
23 and a lot of events listed there are quite
24 explainable. One, an incubator went down. I think
25 there were 40 or something blood samples just lost in

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1 one event by an incubator going down overnight.
2 Another one was at one of the trial sites and the lady
3 had been there to collect the blood samples, slipped
4 on the snow, on the ice, and broke them all. Yes,
5 there's a few things like that.

6 You do see occasional blood samples where
7 the people haven't shaken the heparin tube and you get
8 blood clots. There's no point in running that sample.

9 You do see occasions where a phlebotomist
10 has not collected sufficient blood to do it. Quite
11 commonly, people think, "Oh, I've got a mil in there.

12 We'll take the tube off now and do the next person."

13 That is an occasional thing. It's just a matter of
14 training individuals to say we need at least 5 ml of
15 blood in the tube.

16 DR. LEWINSOHN: And then some of the
17 requirements are fairly tight. For example,
18 incubating the blood within the first 12 hours, is
19 that an issue for places that don't have a 24-hour
20 lab?

21 DR. ROTHEL: I think it probably has got
22 some issues in some settings, yes. Situations where
23 there's a path lab associated with a hospital nearby,
24 that's not an issue at all. It's quite a normal sort
25 of practice. If you're out in the middle of -- we

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1 call it "the Outback"; I don't know what you call it
2 here -- if you're out in the middle of there --

3 DR. LEWINSOHN: Oregon.

4 (Laughter.)

5 DR. ROTHEL: Yes, Oregon, okay. If you're
6 out there and you collect a blood sample in some
7 remote country town with no pathology lab, yes, it
8 would probably be an issue to get it to the local town
9 by then. But you've got to remember, too, the
10 screening generally happens at large institutions.
11 It's not something the local GP generally does to you.

12 DR. LEWINSOHN: I have two more questions.

13 CHAIRMAN WILSON: Go ahead.

14 DR. LEWINSOHN: My other question had to
15 do with the issue of BCG. I was just going over the
16 paper that was published where you gave the medical
17 students BCG. While most people had a quantifiable
18 rise, I guess it was about 15 percent that actually
19 would have been interpreted as going from negative to
20 positive in that regard, and that was just one point
21 in time. Your argument is that perhaps QuantiFERON is
22 better able to distinguish BCG exposure.

23 So my question is, first of all, in those
24 medical students, have you had a chance to look down
25 the road; that is, did their QuantiFERONs come back

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1 down as you might expect? Kind of as a corollary to
2 that, at least we know from the skin test that most
3 people, if they've had at-birth BCG vaccination, will
4 have a negative skin test by the time they're 20 or
5 so. So is there a correlation with age and the
6 likelihood of having a test that's TST
7 positive/QuantiFERON negative?

8 DR. ROTHEL: Yes, that group, I agree,
9 there were about 15 percent positive by QuantiFERON
10 and I think 12 percent or something positive by the
11 TST. Interestingly, though, different people. But,
12 no, we haven't had a chance them up, the short answer.

13 To give you a better answer to the
14 question, in the Streeton study, out of 478 in the
15 low-risk group, in the zero group, roughly 200-or-so,
16 off the top of my head, came from Dr. Jonathan
17 Streeton's practice. They're Australian-born
18 individuals of various ages, and BCG vaccination was
19 routinely used in Australians about 13 in years of age
20 or 16 in 1994. So anyone of the appropriate age had
21 been BCG-vaccinated.

22 Of those 200 that Jonathan recruited into
23 that low-risk group, I think it was around about a
24 third were BCG-vaccinated. There was absolutely no
25 effect of BCG vaccination comparing them to the other

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1 individuals that hadn't received BCG. They were
2 looking at a longer timeframe rather than this five-
3 month experimental period we used.

4 DR. RADFORD: I might also ask Dr. Damien
5 Jolly, who is a consultant statistician for Cellestis,
6 as he has a comment to make on this subject, if that's
7 okay.

8 DR. JOLLY: My name is Damien Jolly. I'm
9 employed by Deacon University in Melbourne, Australia.
10 I work as a consultant for Cellestis Proprietary
11 Limited. I have purchased shares in that company.

12 I would like to address the question asked
13 by Professor Carache particularly with respect to the
14 table on page 77 of the provided pack, because I'd
15 like to direct your attention to page 2-196 in the
16 appendix quite a way through, appendix 2, page 196.
17 In this title you'll find the complete breakdown of
18 the WRAIR dataset by cutoff at 10 percent of
19 QuantiFERON in human response, 15 percent QuantiFERON
20 response, 30 percent QuantiFERON response, and also
21 stratified by the various risk groups within the WRAIR
22 dataset.

23 You'll notice that in these tables all the
24 numbers in the middle column add up to exactly the
25 numbers that are presented on page 77, which was the

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1 title which concerned you. The column on the right
2 provides all the data for the cutoff at 30 percent,
3 which provides the actual concordance and discordance
4 data at the level of 30 percent.

5 I submit this, Mr. Chairman, simply for
6 the point of clarification.

7 CHAIRMAN WILSON: Thank you.

8 Dr. Charache?

9 DR. CHARACHE: I think that's very
10 helpful. As I said, I'm looking for a way of having
11 this available without the false positives. I'm
12 wondering about the possibility of using that same
13 cutoff for all risk factor groups.

14 The reason for changing the millimeters is
15 based on positive predictive value. If we looked at
16 it from the same perspective, I'm wondering if it
17 would be of value to correct in a similar manner all
18 groups, because you can see, even in the high group,
19 you see a similar degree of change. So that's one
20 among my question, is whether this is really set in a
21 way that would avoid false positives.

22 CHAIRMAN WILSON: Okay. Dr. Ng?

23 DR. NG: I think my question is for Dr.
24 Catanzaro. One of the arguments in favor of this test
25 is the 30 percent no-show rate for the second reading

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1 of the TST. I'm assuming you want -- let me restate
2 this. People who come back to get their TST read is
3 often a surrogate for those people who will continue
4 to be followed and be tracked, et cetera. So my
5 question to you is, of that 30 percent who do not
6 return, how effective is the public health system in
7 identifying these people and following them and being
8 able to track them down, if they don't return for this
9 appointment?

10 DR. CATANZARO: Well, it depends
11 completely on the clinical situation. As I said, I
12 work at UCSD Med Center. We basically have no ability
13 to follow people up and go out into the community. On
14 the other hand, the Health Department is very much
15 structured to do exactly that. I think, frankly,
16 that's where this really makes a difference because,
17 if you skin test 100 people, you can expect perhaps 10
18 or 15 percent, depending on the setting, to be
19 reactive. To focus in on those individuals needing
20 followup is to reduce the workload dramatically. I
21 think that that's where this kind of test plays a very
22 strong role.

23 A similar situation is prisons, where
24 there are a large number of inmates that come through
25 that system and often leave the system fairly

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1 promptly, depending on whether you're in a prison,
2 jail, et cetera. Again, it's a matter of following up
3 a small number of individuals rather than following up
4 everybody.

5 I think you're completely right as
6 returning for a reading being a surrogate of taking
7 the pills on your own. The CDC has been stressing to
8 a very great extent observed therapy under various
9 situations -- in prisons, in substance abuse centers,
10 in mental health situations. In each of these
11 situations, knowing that the population you're dealing
12 with is -- or focusing in on the target population --
13 is to eliminate a large part of the workload. So
14 that's how I see the applicability of a one-time
15 measurement being better than a two-time measurement,
16 even though I quite agree with you that returning for
17 a reading is a surrogate for whether you'll return for
18 treatment.

19 DR. NG: So then you have no information,
20 in your example, if you had 100 people skin tested, 30
21 don't return, how effective the system is at finding
22 those 30 to get the second reading?

23 DR. CATANZARO: That's correct, I have no
24 information. I submit it will be different in each
25 setting.

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1 CHAIRMAN WILSON: Dr. Baron?

2 DR. BARON: I just have a quick question
3 about non-tuberculosis mycobacteria other than MAC.
4 We see a lot of kansasii and chelonae and that sort of
5 thing in our setting. Have you looked at the results
6 in those patients?

7 DR. ROTHEL: No, we haven't looked at that
8 yet. I think it's very difficult to find those
9 patients. I'd be interested in speaking to you later
10 to see if we can do a study. That's a very rare
11 event, from my knowledge.

12 But the best information we have there is
13 from the bovine model, where we experimentally
14 infected animals with kansasii as well M. avium, if
15 you remember, and animals with kansasii came out with
16 the avian profile in the QuantiFERON, all above or
17 equivalent in the QuantiFERON test.

18 CHAIRMAN WILSON: Dr. Cockerill?

19 DR. COCKERILL: I think this is in the
20 data, but I was trying to determine this. This is an
21 interesting slide here. When clinicians look at
22 patients with tuberculin skin tests, even a 5-
23 millimeter skin test can be considered positive for
24 latent TB based on, I believe, the CDC criteria. It
25 would be interesting to see specificity comparing the

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1 QFT to the TST when it is interpreted as a positive
2 based on the CDC criteria, whether it be 5 or 10
3 millimeters. Fifteen, as I understand, is a positive,
4 regardless of what the patient presents at, the point
5 being that in groups one or low-risk groups you will
6 find a 15-millimeter induration. As we focus on these
7 various groups, I don't want to lose track of what the
8 comparison is to "a standard" that may not be a gold
9 standard, and by virtue of criteria that have to be
10 developed to interpret it, we have some sort of gold
11 standard. How does this stack up compared to the
12 interpretation of 5 versus 10 versus 15?

13 DR. ROTHEL: All of the data that I've
14 presented for the TST was done by a risk-stratified
15 cutoff, which is the CDC guidelines cutoff. In the
16 panel pack you have data presented to you using a 10-
17 millimeter cutoff. Then there's also something called
18 risk-stratified cutoff. That's precisely using the
19 CDC ATS-recommended cutoffs for the TST.

20 DR. COCKERILL: So the positive 5-
21 millimeter in the charts was a 5-millimeter that was
22 interpreted as a true latent state based on the CDC
23 criteria or was it just the measurement?

24 DR. ROTHEL: The CDC criteria suggests
25 that for people that are TB suspects you use 5

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1 millimeters; for people suspected of latent TB, having
2 risk factors for latent TB infection, you use 10
3 millimeters; for people with no identified risk factors,
4 you use 15 millimeters. Those are the cutoffs we have
5 used for those respective groups.

6 DR. COCKERILL: Okay. So a 5-millimeter
7 patient, if they come and they're 5 millimeter
8 induration, if they don't fulfill criteria for a
9 positive interpretation of that CDC criteria, that was
10 not included as a positive?

11 DR. ROTHEL: No. So individuals at risk
12 of latent TB, if they had a 5-millimeter reaction,
13 would be deemed as negative.

14 CHAIRMAN WILSON: Dr. Beavis?

15 DR. BEAVIS: I had a question about your
16 slide 31. It's also presented in the data packs that
17 we received. It concerns the cutoff for the percent
18 avian difference.

19 My understanding as to how that was
20 determined is that you've got people with known TB,
21 known MAC, and then drew a line trying to discriminate
22 between the two groups. It was Dr. Wood, he said it
23 beautifully. He said that adjusting the cutoff
24 depends on the goal.

25 I was wondering what your thoughts were

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1 and how you picked the cutoff for this. Because
2 you're not calling any of the people with known MAC
3 positive for TB, but you are leaving a couple of
4 people off who are TB-positive and calling them
5 negative. I realize it's overlapping groups, and no
6 matter where you set the cutoff, you're going to wrong
7 in some of the patients. But if you could give me a
8 little bit of your thought process with that, please?

9 DR. RADFORD: We haven't anything in here
10 to sort of address that in the active TB groups, but I
11 would say that the general thrust was to actually
12 include all positive TB cases rather than to diagnose
13 MAC infection. What we're trying to do is to exclude
14 those that we can have a very strong assurance of are,
15 in fact, MOTT-reactive rather than TB.

16 Now what we've done, and I think it might
17 be in the panel pack as well, or is it?

18 DR. ROTHEL: No, I don't think it is. Oh,
19 yes, it is, a graph.

20 DR. RADFORD: I have a graph here that
21 looks at the use of avian at different cutoff levels
22 in patients in the CDC study with active tuberculosis,
23 culture-confirmed.

24 What we see, applying the minus 10 percent
25 avian in different cutoffs, is that there is in fact a

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1 very large threshold. We could, in fact, increase the
2 avian difference a great deal more before we start
3 losing sensitivity for TB. So there is an argument to
4 be made we have not put a stringent enough threshold
5 on, but in the studies we've seen today we believe
6 that it's better to diagnose tuberculosis than to
7 identify a MOTT reactor. So, again, that's another
8 reason for discordance that could occur in the test.

9 DR. BEAVIS: So are you saying that you
10 would consider changing that cutoff for minus 10
11 percent?

12 DR. RADFORD: This is the best cutoff
13 we've had to date, and the data we have supports it,
14 and we believe it does. We have that original study
15 that does support that. It's done in patients which
16 actually have an immune response in many cases; other
17 patients with MAC responses are immunocompromised.

18 DR. BEAVIS: I just want to be clear, make
19 sure that we're in agreement. I guess it's always the
20 case with any laboratory test, when you have two
21 overlapping groups, that no matter where you put your
22 cutoff, you're going to misclassify some patients. In
23 this particular situation one has the option of
24 calling some TB patients negative or you can call some
25 MAC patients positive for TB. The way that the cutoff

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1 was made, it seems that the choice is made to make the
2 error of calling some of the TB patients negative
3 rather than MAC patients positive.

4 DR. RADFORD: If I can just add something,
5 yes, it does like that from that original study we
6 did. We set at a minus 10 percent, but that cutoff
7 was then being used in all subsequent studies we have
8 done. The best example is probably when we've got a
9 gold standard, which is individuals with culture-
10 confirmed TB disease. We haven't missed any, from off
11 the top of my head. I have to check the figures. I
12 don't think we've missed any individuals with a
13 culture-confirmed TB disease due to them having an
14 avian difference less than minus 10 percent.

15 DR. BEAVIS: Of minus 10 percent?

16 DR. ROTHEL: Of less than minus 10
17 percent, yes.

18 DR. BEAVIS: Okay.

19 DR. RADFORD: Well, to be absolutely
20 correct, if you'll see my graph there, we missed one.

21 If we had gone down to minus 40 percent --

22 DR. BEAVIS: Exactly.

23 DR. RADFORD: -- we would have had one
24 more.

25 DR. BEAVIS: Okay.

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1 CHAIRMAN WILSON: In light of our need to
2 stay on a tight schedule today, we only have time for
3 a couple of more questions.

4 Dr. Nolte?

5 DR. NOLTE: I'd like to follow up on the
6 percent avium difference. Basically, has the data
7 been analyzed if you didn't consider the percent
8 avium? I mean I'm trying to figure out what the
9 effect is on the overall test in terms of having this
10 additional component, because there's little data
11 presented to the panel that documents its
12 effectiveness in avium or MOTT-infected individuals?
13 Do you know what I'm trying to get at?

14 DR. ROTHEL: Yes. I know where you're
15 coming from. We've got a slide to address that.

16 DR. NOLTE: I mean, does it contribute?

17 DR. ROTHEL: Yes, that contributes greatly
18 to specificity.

19 DR. NOLTE: I'm sorry?

20 DR. ROTHEL: That contributes greatly to
21 specificity.

22 DR. NOLTE: Greatly? Yes.

23 DR. RADFORD: What I have here, I've got
24 more slides, looking at two different groups, three
25 different groups, and illustrating the effect on

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1 sensitivity and specificity.

2 What we can see here -- and we're looking
3 at the high-risk individuals in this top group, and
4 we're looking at it with a range of various percentage
5 differences cutoff, and "no ADCO" there refers to no
6 avian difference supplied at all.

7 What you really have to look at, when you
8 look at those tables, is think about it in terms of
9 those two-by-two tables we described. The number of
10 PPD positive, QuantiFERON positives in the CDC at-risk
11 group up there is reflected on the NOAD code 158. So
12 that's actually a rise from 145, I think, in the
13 original figure to 158.

14 What we see, though, here is a TST-
15 positive QuantiFERON negative at 70 percent, where it
16 should be, but the QuantiFERON positive/TST negatives
17 rise substantially from a figure -- actually, I think
18 it was 80, my recollection, 72, sorry, up to 122. So
19 we're getting 50 more QuantiFERON positives if we
20 don't apply the avian difference level.

21 I think that generally is reflected in
22 most of the data. We lose sensitivity -- sorry, we
23 lose specificity. We do, in fact, maintain
24 concordance. In fact, it's quite interesting to see
25 that you actually can get a better concordance with

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1 PPD to some degree by actually doing this, but, of
2 course, you do get these QuantiFERON positives at a
3 higher level.

4 DR. NOLTE: Again, with the avian
5 difference, the only patients that were documented
6 avian infections are the 10 or 15 or so children that
7 were described in the packet insert?

8 DR. RADFORD: That's correct.

9 DR. NOLTE: Obviously, this is not meant
10 as a diagnostic aid for MOTT infection?

11 DR. RADFORD: No, this is not being
12 intended as a diagnostic guide for MAC.

13 CHAIRMAN WILSON: Okay, time for two more
14 questions.

15 Dr. Lewinsohn?

16 DR. LEWINSOHN: I was very interested,
17 there was a table that's shown on page 48 that looks
18 at a subgroup of patients, I guess it was 39, who had
19 discordant results and where you were able to retest
20 them. I was actually surprised at the numbers that
21 changed their results on retesting. So, for example,
22 if you were QFT-negative, I think there were a total
23 of nine that on retesting became QFT-positive. Also,
24 if you were QFT-positive, I think there were -- what
25 is it here? -- there was a total 21 --

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1 DR. CHARACHE: It's on the last three
2 lines on that page.

3 DR. LEWINSOHN: I think it was a total of
4 21 that changed. So I'm just interested to know what
5 your thoughts about what accounts for those test
6 changes. Obviously, the TST changed in some cases as
7 well.

8 DR. ROTHEL: To be honest about my
9 thoughts, I can't really glean anything from it. It's
10 a terribly biased population of individuals. They had
11 discordant results initially to start with. To really
12 do this study, you need to do individuals that had
13 concordant results, both positive and negative
14 concordant results.

15 There's only a very small number of the
16 individuals that were meant to be done who had this
17 done. The biggest factor is: What is the effect of
18 having a prior TST on the QuantiFERON test? We've
19 done that in cattle, and we've shown that initially it
20 depresses responses to subsequent QuantiFERON tests
21 and then boosts them for a while, and then past 30
22 days they come back down to normal. We haven't done
23 that in humans, but it's just to me some data we have
24 to present in here because it was in the protocol, but
25 it's somewhat irrelevant.

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1 DR. RADFORD: To perhaps answer your
2 question as to whether or not it actually relates to
3 the stability of the test, we actually do have data
4 presented showing reproduction of the test in
5 individual --

6 DR. LEWINSOHN: No, I was more interested
7 in the issue of interference between the TST and the
8 QuantiFERON and as to whether you would, as part of
9 your advice to clinicians, tell them to one or the
10 other, or if they were interested in doing both, to do
11 one first and then the other?

12 DR. ROTHEL: A good point. I think you've
13 raised something I must admit we hadn't thought of,
14 that you should advise people if they perhaps are
15 going to do both tests. I don't know why you'd want
16 to do that, but if you were going to do both, yes,
17 you'd want to do QuantiFERON before placing the TST.

18 CHAIRMAN WILSON: A final question, Dr.
19 Reller?

20 DR. RELLER: I work in North Carolina,
21 where the prevalence is considerably higher than --
22 we're in the upper quartile nationwide. So it's more
23 than 10 per 100,000. Smear-positive patients, to give
24 some feel for the magnitude of MOTT infections, it's
25 about four or five to one; that is, if we have a

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1 smear-positive, it's far more likely to be. Some of
2 those patients, it's controversial what constitutes
3 disease.

4 So in that sort of population, how would
5 you expect this test to work? Do you have any
6 experiences, is it even possible by looking at the
7 other side of things, the response to the avium
8 antigen stimulation that one might even be able to,
9 owing to the response, separate out those people who
10 have real disease with MOTT versus those who are
11 simply colonized?

12 So there's two parts. One is, how would
13 you expect the test to perform in our area and what
14 about its use from a totally different perspective?

15 DR. ROTHEL: I would expect the test to
16 perform quite well in your area in discriminating
17 between the two infections. As far as looking at
18 disease, that's specifically what that study was done
19 that we used to establish the percentage avian
20 difference cutoff, the paper by Stapledon, et al.,
21 which is appended in your panel packet, physicians
22 working in Adelaid. They wanted to use the test to do
23 exactly what you're talking about, discriminate
24 between disease caused by TB or MOTT bacterium avium
25 complex.

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1 They found in that data they would use a
2 different cutoff to do that interpretation. That's
3 not what we're proposing the test for, of course, in
4 this situation, but it discriminated 100 percent, I
5 think is the conclusion they drew in that paper.

6 Again, it's a limited study, and I think
7 for that application we need to do obviously vastly
8 more work, but I think it's got applications there.

9 CHAIRMAN WILSON: Okay, while the FDA is
10 getting their presentation materials together, let's
11 take a very brief break, about five minutes.

12 (Whereupon, the foregoing matter went off
13 the record at 10:44 a.m. and went back on the record
14 at 10:54 a.m.)

15 CHAIRMAN WILSON: Okay, I'd like to
16 reconvene the meeting at this time, please.

17 At this point we'd like to move on to the
18 FDA's presentation. Again, I'd like to ask the panel
19 members to hold any questions until all three
20 presentations are complete. I'd like to remind the
21 audience that only panel members can ask questions of
22 the speakers.

23 FDA, the first presentation will be given
24 by Roxanne Shively, who is a Senior Scientific
25 Reviewer for the Bacteriology Devices Branch.

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1 MS. SHIVELY: Good morning. It's kind of
2 hard coming after such good discussions have already
3 opened up a lot of issues.

4 For FDA, the QuantiFERON-TB application is
5 a multi-level endeavor. Not only is there a bridging
6 of the continents with Australia here, but within FDA
7 we've had cross-center activity with CDER
8 participation, CBER, and of course CDRH on this
9 review.

10 We really appreciate the company's effort
11 in compiling the panel packages for you and their
12 complete presentation to you this morning.

13 Because of the public health importance of
14 a test for used for diagnosing latent TB infection,
15 FDA review of this application is expedited. We also
16 brought this to the Microbiology Advisory Panel early
17 in the review cycle because we recognize the
18 importance of questions related to evaluating the
19 performance of a new assay when the only current
20 approach, the tuberculin skin test, has considerable
21 limitations. We believe your input will help the
22 company and FDA to most efficiently develop a path for
23 identifying the clinical merits of this assay.

24 Next slide. The first part of FDA's
25 presentation covers the intended use for the

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1 QuantiFERON assay, a brief discussion of in vivo
2 versus in vitro testing, and then some elements of the
3 QuantiFERON analytical performance that we believe is
4 important to the discussion overall today.

5 The QuantiFERON assay is submitted as an
6 aid in the detection of mycobacterium tuberculosis
7 infection. This is the same labeled intended use as
8 tuberculin PPD for in vivo use. The proposed labeling
9 does have limitations, as already mentioned, and we
10 would note that the primary clinical studies did not
11 include these groups, either pregnant women, 17-year-
12 olds, or HIV-positives, other immunosuppressed.

13 I would like to clarify one thing that
14 came up the end of the discussion, that this assay is
15 not submitted to differentiate individuals with MOTT
16 infection. The avium PPD portion of the assay is
17 intended to control for cross-reactivity, and it
18 hasn't been evaluated for differential capabilities.

19 We are at the next slide. Much of the
20 data and information available to characterize the
21 QuantiFERON is relative to skin testing. One of our
22 concerns is how to understand differences that would
23 affect who is tested and how we use the results from
24 the new assay.

25 The areas that I will initially present

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1 look at similarities and differences between these two
2 tests. This slide blocks out in a very simple way the
3 basic elements of the skin test versus the
4 QuantiFERON. The company has already discussed
5 differences here at the pre-analytic level; that is,
6 intradermal injection versus collection of the venous
7 whole blood, and performing the test in the clinic
8 versus performing the test in the clinical laboratory.

9 We would like to point out that one of the
10 cited advantaged that the company makes is that the
11 QuantiFERON assay has the benefit of being a lab-based
12 test that will add greater control and
13 standardization. We will want to look and make sure
14 that that control and standardization within the
15 clinical laboratory is possible, too.

16 The direct common elements between the two
17 tests is the human PPD reagent. That is the same
18 reagent as the tuberculin PPD that's used in the skin
19 testing. Although the two tests use different
20 measures, they essentially are measuring an
21 individual's immuno response. The TST does have the
22 progressive end-points that have already been
23 discussed. As the company has presented, they are
24 proposing to change the cutoff for the QuantiFERON to
25 a scaled differential cutoff based on risk.

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1 I would like to point out that with this
2 cutoff modification that we have encourage the company
3 to look at options with the cutoff, and that the new
4 analyses and data supporting this were submitted
5 within the past two weeks, right at the time of your
6 panel packs. So we wanted you to have this available,
7 but we will be focusing on the original data that was
8 submitted to us, looking at the implications of the
9 tools and how we evaluate comparisons between the two
10 assays and overall performance parameters.

11 Okay, next slide. This slide illustrates
12 the initial immune response at the cellular level and
13 what is being measured by the skin test on top and the
14 QuantiFERON on the bottom. Both assays are detecting
15 components of cell-mediated immunity reacting to
16 antigen that is injected intradermally for the skin
17 test and added to the blood culture for QuantiFERON.
18 The skin test measures a delayed-type hypersensitivity
19 reaction resulting from the interaction of multiple
20 cells, including memory T-cells and the network of
21 cytokines and other immune mediators. The QuantiFERON
22 measures the presence of these memory T-cells, which
23 are down in the dish now, in a venous blood sample by
24 the production of gamma interferon.

25 One other difference at the cellular level

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1 that already came up in the discussion that could
2 affect responses in each of these assays is that, when
3 the PPD is injected intradermally, memory T-cells are
4 recruited to the site of infection; whereas, with
5 whole venous blood the circulating T-cells that are
6 sensitized that are the memory T-cells are already
7 present in the venous draw that is collected. So
8 there's no recruitment.

9 You have already asked about the
10 differences in white cell levels and the effect of
11 those levels on QuantiFERON results. We would
12 certainly welcome your comments on the need to look at
13 that type of data to qualify and standardize this
14 assay, too.

15 Next slide. The next few slides highlight
16 some of the things we know about skin testing
17 accumulated from its history of use. Our primary
18 question to you today is going to be, how can we best
19 describe similar attributes for the QuantiFERON and
20 what statistical tools are best to use?

21 The delayed-type hypersensitivity reaction
22 of the skin test is detectable two to twelve weeks
23 after infection. From available research, we would
24 expect gamma interferon to parallel that.

25 Sensitivity of skin testing approaches 100

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1 percent in persons with normal immune responsiveness,
2 but up to 25 percent of infected or diseased
3 individuals we know may be falsely negative. Most of
4 these may primarily be due to HIV immunosuppression,
5 but also certainly the other host variables and
6 problems cited by Dr. Catanzaro.

7 Next slide. Specificity of the TST is
8 improved by increasing the reaction size that
9 separates a positive from a negative reading, and we
10 expect, as Dr. Charache has already pointed out,
11 improved sensitivity using those cut points. We would
12 expect that approximately 95 percent specificity when
13 there is common cross-reactivity in the population
14 with non-tuberculosis mycobacteria. We are including
15 BCG and NTM together as non-tuberculous mycobacteria
16 in this category as potential cross-reactants. When
17 BGC vaccination or NTM is not common, we would expect
18 the specificity to be higher and about 99 percent.

19 Our last point: The TST performance
20 overall, both sensitivity and specificity, is affected
21 by other population variables, too, such as age, the
22 prevalence of disease, and in addition to BCG
23 vaccination and non-tuberculosis mycobacteria.

24 Next slide. We've already discussed using
25 the progressive cut points. These are the joint

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1 CDC/ATS criteria, using 15 millimeters for a low-risk
2 population, 10 millimeters for those with increased or
3 moderate risk, and the smallest cutoff, 5 millimeters
4 -- actually, it's the most stringent -- in the high-
5 risk groups.

6 Next slide. Risk assessments on which the
7 cut points are based are from both epidemiological and
8 clinically-defined groups. I am not going to go
9 through all these, but we did want to have them
10 available because it can get confusing, too. I do
11 want to highlight that the ones in red are those that
12 have the highest risk and would be read at the 5
13 millimeter cutoff. You and refer to Table 7 from the
14 joint statement, too, for the complete listing of
15 these.

16 Next slide. Using gamma interferon as a
17 marker, a post cell-mediated immunity certainly has a
18 solid foundation of research evidence. Besides the
19 importance of gamma interferon in the cell-mediated
20 immune response to MTB infection, reports have shown
21 that production is decreased in patients with active
22 TB, especially those with severe disease. This
23 suppression may last more than a year.

24 We do want to note a word of caution:
25 that the gamma interferon measurements from published

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1 research characterizing responses may not always be
2 comparable, depending upon the host models used, the
3 methods, and types of assay used.

4 Next. I think I am going to skip this
5 slide because I know we are anxious to get through
6 this.

7 I am going to go to the basic analytical
8 portion of the QuantiFERON as detecting gamma
9 interferon. Gamma interferon is estimated for each of
10 the four harvested plasma samples, and this is done
11 from an EIA standard curve using the kit standards
12 which are provided in the kit. These are zero, low,
13 medium, and high standard.

14 There are acceptance criteria for using
15 these standard results. Again, I won't go through
16 these, but they are critical because they are the only
17 controls applied to the EIA portion of the QuantiFERON
18 and there is no independent control material in the
19 kit outside of the kit standards themselves.

20 Next slide. Okay, the QuantiFERON kit has
21 no external control materials, and also the labeling
22 doesn't recommend any external control materials that
23 could be tested. Instead, the labeling recommends for
24 QC that the acceptance criteria for the standard curve
25 be used and also adherence to recommended procedures,

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1 and that following these procedures and using the
2 curve acceptance criteria will contribute to control
3 of the assay.

4 The design of this assay does, however,
5 have an internal control, and that is the mitogen-
6 cultured sample that is supposed to control for
7 functionality of blood cells to produce gamma
8 interferon. Another design aspect of the assay is the
9 nil control, which essentially would control for
10 background of gamma interferon activity in the patient
11 sample. This is value is acceptable whether it is
12 zero, less than zero, or greater than zero.

13 Although we would expect this value to be
14 almost always zero, the nil result is subtracted out
15 as background regardless. We do understand the
16 importance of both the mitogen and the nil for getting
17 reliable results with this assay, but we do question
18 whether they are sufficient for ensuring reproducibly
19 reliable results in clinical laboratories. We have
20 put that question to you today.

21 Next slide. Oops, I'm sorry, that's it.

22 The decision thresholds are cutoffs for
23 the QuantiFERON assay, and how those cutoffs are
24 calculated has already been described by the company.

25 The discussion has already rapidly moved forward on

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1 modifying these cutoffs and looking at variables that
2 affect the cutoffs.

3 So I am not going to linger here, but I do
4 want to point out that basic principles that are used
5 in these studies may affect the outcome of the study
6 and what cutoff chosen. The major question is whether
7 the cutoff will be applicable to other populations
8 other than the one where the initial study was done.

9 For the human response cutoff, the
10 Australian guidelines are slightly different than
11 those used in the U.S. Only nil values greater than
12 zero were used in the calculations, and mitogen
13 results less than 0.5 rather than 1.5 were considered
14 indeterminate. We would ask whether any of these
15 factors could affect use of this cutoff in other
16 populations.

17 The same for the percentage avium
18 difference. The study was originally done to show the
19 difference between a group of children who had been
20 infected with MOTT and a larger group of adults who
21 had had TB disease. Again, we would question whether
22 this cutoff would apply to general other cutoffs for
23 controlling the level of cross-reactivity in
24 populations.

25 One final cutoff that we consider to be

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1 important is the mitogen minus nil because it's this
2 value that distinguishes whether an assay will be
3 indeterminate or will be valuable in the QuantiFERON
4 test.

5 We would note that, regarding this
6 mitogen, in order to get a 15 percent human response,
7 you would need to have at least a 10 international
8 unit reading with the mitogen.

9 Next slide. The last area I want to cover
10 this morning is reproducibility. There have been
11 various studies presented by the company to support
12 inter- and intra-assay reproducibility. As pointed
13 out already, there are appreciably difficulties with
14 designing these studies because of the nature of the
15 assay itself.

16 We are going to look at the one study that
17 we consider to be very good in that it looks at inter-
18 laboratory reproducibility. We did not have inter-
19 laboratory reproducibility established during the
20 clinical studies. So this is an area that concerns
21 us, to be able to ensure that the test can be done
22 reproducibly in different laboratories.

23 The data is up here, and the table was
24 done using 50 duplicate blood specimens tested at two
25 different sites in Australia. If you look at the

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1 table, the majority of the samples tested were
2 positive in the QuantiFERON, gave an agreement of 98
3 percent, Kappa .89, with an ICC of .94. Even though
4 the agreement is good in this study, we would question
5 whether we would see the same type of data when you
6 have more negative results.

7 Because of our concerns with controls and
8 not having inter-lab reproducibility across the range
9 of the assay, we also are concerned that results from
10 the clinical studies may possibly be affected by
11 inter-laboratory variations. We would certainly
12 welcome your suggestions in the discussion for
13 bridging that concern.

14 Next slide. There are additional
15 supportive data from published and unpublished
16 literature with comparisons of QuantiFERON and skin
17 tests. These include testing different or selected
18 populations, and the company has discussed some of
19 these this morning. These also include the Bovigam
20 studies done using the assay that's very similar to
21 the QuantiFERON but does have different reagents and a
22 different methodology.

23 Also, we would note regarding the studies
24 in animals that there is a different host, a different
25 pathogen, and different tests were used. We would

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1 again welcome your comments on how to position these
2 additional studies into the wealth of information that
3 we have from the clinical studies, and even further,
4 how to statistically evaluate those assays and derive
5 some meaningful statistics from that data.

6 Next slide. Dr. Leonard Sacks will be
7 covering the clinical studies in the next minute.
8 Before ending, I do want to point out that there are
9 differences, very small differences, between the
10 published CDC data and what is being presented here.
11 Also, of course, we are going to be looking at some
12 new data today using the 30 percent cutoff. As I
13 mentioned before, this has been very recently
14 submitted. We would encourage you all to consider how
15 we can best look at this proposal and the new analysis
16 done, and how we should validate new cutoffs to be
17 used in the different calculations.

18 So I'll turn it over to Dr. Sacks now.
19 Thank you very much.

20 DR. SACKS: Good morning. My name is Dr.
21 Sacks, Leonard Sacks, from the Division of Special
22 Pathogens, and I will be spending the next
23 approximately ten minutes reviewing the clinical use
24 of QuantiFERON as an assay for tuberculosis. I will
25 be restricting my presentation to the two pivotal

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1 studies that were submitted by the applicant.

2 Can I have the first slide, please?

3 Just a bit of background, and I think a
4 lot of this has already been covered and most of the
5 audience is familiar with it. But there are several
6 ways in which people respond to exposure to
7 tuberculosis. These may range from no detectable
8 response through simple skin test conversion and self-
9 limited primary complexes developing in the lung with
10 or without positive skin tests. Then there are a
11 couple of responses which may result in overt or
12 active TB, the primary progressive TB, as a result of
13 the initial exposure or reactivation subsequently once
14 exposure has already occurred. It is really in the
15 first three categories that latency becomes an issue.

16 This is the area where QuantiFERON has proposed its
17 utility.

18 Let's go on to the next slide. These were
19 the intended uses of QuantiFERON as submitted in the
20 original application. It was to be an aid in the
21 detection of latent mycobacterium tuberculosis
22 infection. There were a couple of other points that
23 were included.

24 First of all, that a negative result does
25 not preclude active tuberculosis. Second of all, that

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1 the QuantiFERON tests may be inconclusive in immuno-
2 compromised or immunosuppressed individuals and those
3 with no cellular or impaired cellular immune response
4 to tuberculin. Finally, that the safety and the
5 effectiveness of this test was not established in
6 individuals under 17 years of age and in pregnant
7 women.

8 Let's go on to the next slide, which again
9 reiterates some of the points that were very
10 adequately made early on, but there is no gold
11 standard for the diagnosis of latent tuberculosis.
12 The tuberculin skin test is one of the methods or one
13 method that is used to detect latency. The tuberculin
14 skin test allows the institution of prophylaxis to
15 prevent reactivation in patients having a positive
16 test, and that's how it is conventionally used.

17 The tuberculin skin test is fraught with
18 problems. As we know, it is an archaic test. It has
19 problems with sensitivity, particularly in patients
20 who are immunosuppressed or such as HIV-positive
21 patients or patients on steroids, et cetera. It has
22 problems with specificity related to infections with
23 mycobacteria other than tuberculosis, and it has the
24 well-recognized practical limitations of compliance.
25 Patients have to come back for a re-read after 48 to

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1 72 hours. There is some subjectivity in
2 interpretation of the size of the induration. There
3 is some discomfort in the application.

4 The last point to be made here is that
5 only a small proportion of TST-positive patients will
6 actually develop TB, approximately a 10 percent
7 lifetime risk.

8 Let's go on to the next slide. Now in the
9 absence of a gold standard, what methods can we use to
10 evaluate a new diagnostic test for latent
11 tuberculosis? What I have done is just put up a
12 couple of suggestions. There are obviously many other
13 different ways in which this can be approached.

14 First of all, one could contemplate a
15 prospective study to determine the ability of a
16 positive test to predict active tuberculosis. Another
17 method would be to compare with existing diagnostics
18 for the diagnosis of latent tuberculosis. The third
19 suggestion would be to correlate the performance of
20 the diagnostic test with the clinical risk for
21 tuberculosis. It is the latter two approaches that
22 have been used by the applicants.

23 Let's go on to the next slide. There,
24 too, pivotal studies, one performed in collaboration
25 with Walter Reed, one performed in collaboration with

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1 the CDC, these were roughly the inclusion and
2 exclusion criteria. The Walter Reed studied included
3 naval recruits. It was a single-site study based in
4 Illinois at a recruiting center, although the actual
5 enrollees were from all over the country. They were
6 to be HIV-negative.

7 The CDC study, to some extent this was a
8 clinic-based study, a multi-center study on clinic
9 subjects presenting for screening with tuberculin skin
10 tests. It was a five-center U.S.-site study, as was
11 mentioned before, in Massachusetts, Maryland, two
12 sites in California and New Jersey. Patients over 18
13 years of age, also HIV-negative, and non-
14 immunosuppressed.

15 So there were a lot of similarities but
16 some differences between these studies. They do seem
17 to reflect the demography of patients who would use
18 this test.

19 Next slide. Just to give you some idea of
20 the numbers, initially, there were 1,627 enrolled in
21 the CDC study, 1,961 in the Walter Reed study, a total
22 of over 3,000 patients; quite a number of exclusions,
23 670 in all leaving, approximately 3,000 evaluable
24 patients when both studies were pooled.

25 Let's move on to the next slide. Just a

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1 word about patients excluded from the analysis. We
2 did note that almost 20 percent, 19 percent, of all
3 enrollees were excluded. There were 144 patients
4 excluded at a single site in the CDC study, and this
5 was apparently on the basis of unverifiable informed
6 consent. The other reasons for exclusion were also
7 mentioned earlier. Some of them were technical
8 errors, incubator failure, the TST was not read at the
9 right time or not read at all.

10 Let's move on to the next slide. This
11 just gives you an outline of the demographics in both
12 of these studies. In the CDC studies we see that this
13 was a slightly older population. The mean age was 39
14 compared to 20 in the Walter Reed study. There were
15 more females in the CDC study, 49 percent, and only 17
16 percent in the Walter Reed study. There was a higher
17 representation of black persons in the CDC study,
18 whereas 56.3 percent of the patients in the Walter
19 Reed study were white.

20 Let's move on to the next slide. In
21 practice, there were seven embedded subgroups within
22 these two big studies, each consisting of different
23 risks for development of tuberculosis. What I have
24 done in this slide is I have ranked these subgroups
25 for both studies according to increasing risk for

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1 tuberculosis as we go down the table.

2 So in the first Walter Reed subgroup there
3 were 397 patients with no identified risk for
4 tuberculosis, and a similar group of 98 patients in
5 the CDC study, again with no identified risk. It was
6 a low-risk group of 1,066 patients in the Walter Reed
7 study from the U.S. state with a TB incidence of
8 greater than 10 per 100,000. Then there were two
9 subgroups here which represent the population where
10 TST is often used to decide on prophylaxis. Two
11 thirty-two patients were in the Walter Reed study who
12 were TB contacts who came from countries where TB was
13 prevalent, and a similar group over here, TB contacts,
14 persons from countries where TB was prevalent:
15 patients from shelters, intravenous drug addicts, and
16 others.

17 Finally, there were two categories at the
18 bottom where the risk of TB was appreciable. In group
19 three these were patients with pulmonary symptoms
20 which were compatible with those who were evaluation
21 for tuberculosis. In the risk group four these were
22 patients who had had previously cultured-confirmed
23 tuberculosis and had completed therapy.

24 Now the next slide demonstrates the
25 comparable performance of the tuberculin skin test and

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1 the QuantiFERON test. Let me just mention that for
2 simplicity and a couple of other practical reasons
3 which I will mention, I have used the 10-millimeter
4 cutoff for the tuberculin skin test across the board.

5 I thought that this was an equitable comparison
6 because QuantiFERON doesn't use a ranked cutoff, so I
7 have used the 10-millimeter for that reason. That is
8 also the cutoff that people would defer to in the risk
9 categories.

10 Here what we see is that in the low-risk
11 populations up here, these are populations with no
12 risk for tuberculosis. We see a tuberculin skin test
13 positivity of somewhere between 1 and 4 percent,
14 whereas the QuantiFERON is appreciably higher, between
15 5 and 8 percent.

16 When we look at the middle risk group, we
17 see that the QuantiFERON and the tuberculin skin test
18 positive rates are somewhat similar. In fact, in this
19 particular group, CDC risk population two, 24 percent
20 and 23 percent. When we move into the higher-risk
21 categories of either confirmed or suspected
22 tuberculosis, it is clear that tuberculin skin tests
23 are much more frequently positive than QuantiFERON
24 tests, 84 percent in the tuberculin skin test group,
25 70 percent in the QuantiFERON. In patients with

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1 previous confirmed tuberculosis, 92 percent positive
2 by TST, 64 percent positive by QuantiFERON.

3 Let's move on to the next slide, which
4 just shows the same information graphically. What I
5 have done here is I have the increasing risk for TB
6 along the X axis and the percentage positive by each
7 of the two tests on the Y axis. I think it is quite
8 clear that both of these tests correlate with
9 increasing risk for tuberculosis, but there are some
10 differences, and I am going to concentrate on those
11 now.

12 Let's first take a look at this area of
13 the curve. Let's go on to the next slide. How about
14 the performance in high-risk populations? Well, we
15 can see that there is clearly differences in
16 sensitivity for the two tests in patients with
17 confirmed tuberculosis.

18 Now it has been mentioned earlier that
19 there are reports that gamma interferon is decreased
20 in patients with active tuberculosis disease. The
21 effect of this finding on the sensitivity of
22 QuantiFERON in other risk groups is really unclear.

23 How about this section of the curve?
24 Let's move to the next slide. What we are addressing
25 here is the performance in low-risk populations. Now

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1 here, although the apparent difference is small, these
2 are the patients who would qualify for TB prophylaxis
3 over here.

4 Now just bear in mind that, since the
5 lifetime risk of tuberculosis is only 10 percent, many
6 healthy individuals may receive unnecessary therapy
7 with potentially toxic drugs. So our aim would be to
8 maximize the specificity of an assay in this sort of
9 population group.

10 If we look at population one, which is at
11 the end here, TST was positive in 1 percent of the
12 population, and QuantiFERON was positive in 5 percent
13 of the population. So potentially a fivefold
14 difference in the number of individuals qualifying for
15 treatment.

16 What about the middle of the curve? Let's
17 move on to the next slide. The performance in the
18 population for intended use, these are patients with
19 risk factors for tuberculosis: patients from
20 countries with a high incidence of tuberculosis,
21 patients from shelters, and drug users.

22 I would like to draw your attention to
23 population group five. I have mentioned these a
24 little earlier. Here both tests look strikingly
25 similar, and the question we are left with is whether

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1 the 23 percent that are positive by QuantiFERON in
2 this group are the same individuals as the 24 percent
3 that are shown to be positive by tuberculin skin
4 tests.

5 The next slide addresses this in some
6 detail. This may be a little confusing. These are
7 not completely drawn to scale, but let me just
8 orientate you.

9 This is CDC risk group two, intermediate
10 risk for tuberculosis, 944 patients in total.
11 Tuberculin skin test cutoff has been set at 10
12 millimeters. What we see here are those positive by
13 QuantiFERON are in this circle; those positive by
14 tuberculin skin tests are in this circle. Those
15 negative on both tests are out here.

16 So we see that 68 percent of the
17 population are negative on both tests, but we can
18 clearly see that there is a discordance between the
19 patients that are detected positive by TST and those
20 that are detected positive by QFT. What we can see
21 that, if you did a QFT, a third of the QFT-positive
22 patients would not be TST-positive. Conversely, by
23 TST, a third of the QuantiFERON-positive patients
24 would not be found by TST. So there is a significant
25 discordance even though the absolute percentage of

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1 positive tests in both of those groups appears the
2 same.

3 Let's just look at this sort of analysis
4 for a couple of the other risk groups, the next slide.

5 Now this is the low-risk group, 98 patients with no
6 observable risk or no identifiable risk for
7 tuberculosis. What we see here is TST is picking up
8 less patients; 91 percent or 92 percent approximately
9 are negative by both tests. TST, as I say, is picking
10 up less patients; QuantiFERON is picking up a lot more
11 patients. In fact, almost five-eighths of the
12 patients who are positive by QuantiFERON are not found
13 to be positive by TST. This is in the low-risk group.

14 Let's look at the flip side, next slide.
15 These are patients with confirmed tuberculosis. Here
16 we see that the tuberculin skin test positivity is
17 much higher than the QuantiFERON positivity. The
18 overlap is pretty good, but QuantiFERON is not picking
19 up almost a third of the patients that are picked up
20 by the tuberculin skin test, a very small number of
21 QuantiFERON-positive patients that are not picked up
22 by the TST.

23 Okay, I would like to just change gears a
24 little here. Let's move on to the next slide. This
25 was mentioned a little earlier. I am just

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1 highlighting it as an issue of interest.

2 These were the discordant results
3 reinterpreted, or at least retested by both
4 QuantiFERON and TST. As has been pointed out earlier,
5 this was not a randomized sample. This did not
6 include patients who had concordant results. So I
7 guess, treated with that degree of circumspection --
8 but what we see here is that patients changing from
9 QuantiFERON-negative to QuantiFERON-positive, there
10 were 22 patients who started off QuantiFERON-negative
11 with discordant results and 41 percent of them became
12 positive on retesting. When you do the same thing
13 with the tuberculin skin test in 39 patients who had
14 discordant results, you find that 26 percent of those
15 who are TST-negative changed to TST-positive. So a
16 bigger change in the QuantiFERON.

17 When we look at the reverse, the
18 percentage of patients who changed from QuantiFERON-
19 positive to QuantiFERON-negative, we see that 54
20 percent of the 39 patients became negative after an
21 initial positive test, whereas in the tuberculin skin
22 test it was unusual for patients to become negative on
23 a second reading, only 18 percent or 4 out of 22.

24 Just one other aspect, the next slide,
25 which was also touched upon. These were the results

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1 of a subgroup of patients in the CDC study who were
2 identified as being BCG-positive. BCG, as we know,
3 may itself affect the performance or at least affect
4 the positive rates of the tuberculin skin test. It
5 may also be a co-variable for exposure or risk of
6 exposure to tuberculosis.

7 What we see here in 157 vaccinated
8 individuals was that QuantiFERON was positive in 43
9 percent; tuberculin skin test was positive in 58
10 percent. In unvaccinated individuals, the positive
11 rates were the same for both tests.

12 The next slide just discusses a couple of
13 the thoughts that I had about the qualities of an
14 ideal test for latent tuberculosis. Theoretically,
15 such a test should always be positive in confirmed
16 tuberculosis, should always be negative in patients
17 with no TB risk. It should be negative in other
18 mycobacteria infections. Conversions from negative to
19 positive should correlate with TB exposure. Finally,
20 there should be confirmed value of the test in its
21 ability to predict the development of tuberculosis.

22 As you will notice, a couple of these
23 points have been addressed by this submission.
24 Several of them have not. That may leave some room
25 for discussion.

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1 The next slide just brings me to my
2 conclusions, which were, first, that the sensitivity
3 of QuantiFERON differs from tuberculin skin tests when
4 it is evaluated in patients with confirmed
5 tuberculosis. I do mention again, or remind you, that
6 interferon production is reported to be inhibited in
7 active tuberculosis. The effect of this on the
8 sensitivity of QuantiFERON in other populations is
9 unclear.

10 Next slide. Positive rates for
11 QuantiFERON were higher than tuberculin skin tests in
12 low-risk populations. The pivotal clinical studies
13 did not determine whether this was an indication of
14 poor risk specificity or increased sensitivity of
15 QuantiFERON tests.

16 Finally, just to remind ourselves that the
17 populations identified as positive by QuantiFERON or
18 positive by tuberculin skin test often differed.

19 Thank you.

20 CHAIRMAN WILSON: Thank you, Dr. Sacks.

21 The next presentation will be by Mr. John
22 Dawson, who will present the statistical analyses of
23 the data.

24 MR. DAWSON: Good morning. Thank you for
25 affording me the opportunity to present the FDA's

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1 statistical perspective on this application.

2 I am going to cover two things in my 10
3 minutes or so. First, sensitivity/specificity-type
4 evaluation of performance of QFT relative to TST as a
5 gold standard and, secondly, some measures of
6 agreement and some results using them which may be
7 appropriate if TST is, as we I guess generally agree,
8 not a gold standard.

9 Next, please. The sponsor has in their
10 draft labeling estimates of sensitivity and
11 specificity that derive from the Streeton study, 1998
12 Streeton study. They estimate sensitivity at 90
13 percent and specificity at 98 percent. I have a
14 little bit of a worry about using the Streeton numbers
15 rather than the QFT current study, the PMA study
16 estimates in the labeling, because the percent human
17 response cutoff used in this study was derived in the
18 Streeton study and also used to estimate sensitivity
19 and specificity. When the cutoff is arrived at by ROC
20 analysis, the problem is that performance may be
21 overly optimistic, simply a function of trying to
22 optimize or maximize something about the performance
23 in choosing the cutoff.

24 This a little bit shows up and possibly
25 explains what happens here when I use the PMA data to

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1 estimate sensitivity using the TB suspect category
2 patients, and among those, those that are culture-
3 positive, what I get is an 88 percent estimate for
4 sensitivity compared to the 98 percent in the Streeton
5 study.

6 Specificity using the low-risk group in
7 the PMA data is 92 percent versus the 98 in the
8 Streeton study. I don't know whether this is because
9 of overoptimism, but I am simply pointing out that it
10 is probably not appropriate to use the numbers from
11 the Streeton study in the labeling in place of numbers
12 from the PMA study.

13 Another problem that we have with these
14 estimates, the sensitivity and the specificity, is
15 that they are based on selected parts of the intended-
16 use population, rather small groups at the two
17 extremes, the low-risk group and the TB-suspect group.

18 The problem there is what we know as spectrum bias
19 can be work at here. The largest group of patients
20 were in the intermediate-risk category. We have no
21 justification for assuming that the estimates of
22 sensitivity from those extreme groups would apply in
23 the intermediate-risk group.

24 If there is no gold standard, then we have
25 the option of evaluating agreement between QFT and

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1 TST. Now I want to move to that topic and talk a
2 little bit about agreement. Next, please.

3 This is a depiction of the two-by-two
4 table which you have seen numerous ones this morning.

5 I use the term "agreement" to mean literally on a
6 per-case basis, whenever we have QFT-positive and TST-
7 positive, that's an agreement. If one is negative and
8 the other is negative, that is also an agreement, and
9 the overall agreement derived from a two-by-two table
10 is basically the numbers from the main diagonal of the
11 table divided by the table total.

12 Next, please. Now I want to give you a
13 couple of other definitions very quickly, one of which
14 is expected agreement. The reason for that is that
15 the Kappa agreement statistic, which is the one that
16 the company has chosen as their primary agreement
17 measure, involves both the observed agreement on the
18 main diagonal of the table, expected agreement, and I
19 have to apologize; I have it written as "A plus B over
20 N." It should be "A plus D over N."

21 What is done in getting an expected number
22 is that you set up basically the null hypothesis that
23 the two tests being compared are mutually-independent,
24 and then you use the marginal frequencies, the
25 proportions on the margins of the two-by-two table, to

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1 generate numbers for the four cells of the table,
2 which is what you would expect if the two tests are
3 conditional-independent.

4 I always have the same problem with this
5 statistic in these kinds of method comparison studies
6 because the null hypothesis simply is not reasonable.

7 It makes it very easy to get a statistically-
8 significant result because inherently the methods
9 being compared have some amount of built-in agreement.

10 The Kappa correlation coefficient takes
11 the observed numbers of cases on the main diagonal,
12 subtracts out the expected number of cases on the main
13 diagonal, and then is scaled by one minus the expected
14 frequency.

15 Another measure is agreement with the
16 positive skin test; that is, taking those that are
17 given as TST-positive, what percentage of those are
18 also QFT-positive. Agreement with the TST-negative,
19 you take those that are TST-negative and divide that
20 into the number which are also QFT-positive.

21 We have an agreement index, both a
22 positive and negative variation. What this does that
23 is different than those above is you take the total
24 number of cases that are positive by TST, add that to
25 the total number that are QFT-positive, and call that

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1 an overall number of positive results. Then you take
2 the number that are positive by both QFT and TST,
3 multiply that two, and that ratio then is what we call
4 agreement index positive. In agreement index
5 negative, you get the total number that are negative
6 by either and divide that into the number that are
7 negative by both.

8 Next, please. I am sorry this is such a
9 massive table, but I think I can get you through it
10 pretty quickly.

11 What this does is to compare the agreement
12 between QFT and TST on the various indices just
13 described. Just to orient you on this table, this
14 first part deals with the low-risk group, using the 15
15 millimeters induration for the skin test. This little
16 block over here is the array of the 98 cases in the
17 low-risk category. The plus indicates the test
18 positive; the minus is test negative. The columns are
19 for QFT and the rows are for TST.

20 So we have, for example, 89 cases that are
21 negative by both tests. We have just one case in the
22 low-risk category that's positive by both.

23 Now I have to deal somehow here with the
24 problem that we have with basically any measure of
25 agreement, which is the dependency on prevalence.

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1 That is, prevalence is a confounding factor in any of
2 these measures of agreement.

3 How do we know that prevalence is a
4 problem? We know that because you can take the two-
5 by-two table and write out a probability model of that
6 table in terms of sensitivity/specificity and the
7 probability of agreement between the two tests being
8 compared and prevalence. So you put all those
9 parameters together in a two-by-two table and it gives
10 you what we can an expected number of the four cells
11 in the two-by-two table that you can compare with the
12 observed.

13 Once you have done that, then you are free
14 to fix the parameters sensitivity/specificity in
15 agreement and vary the prevalence. Each time you vary
16 the prevalence, get your expected table and calculate
17 your agreement statistics from it and see if they
18 change, you haven't changed the performance. What you
19 have done is changed the prevalence. Unfortunately,
20 all of these measures undergo a change when you vary
21 the prevalence.

22 Let me just point out the problem that we
23 have with Kappa. It is well-known, established in the
24 literature, and it is easy to show that Kappa, where
25 performance is held fixed, will be very low at the

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1 extremes of prevalence. Very low prevalence and very
2 high prevalence, it will be a low value. You see that
3 17 percent for the low-risk group. That's exactly
4 what we would expect. Then when you go from the low-
5 risk category up to the intermediate-risk and the
6 suspect category, you see that it goes up
7 considerably.

8 So when you see a Kappa that looks good,
9 you need to ask, well, are we looking at a high
10 prevalence population here? If it is, then, well,
11 maybe that's just what you should expect because of
12 the relationship with prevalence.

13 The same thing applies -- let me just
14 quickly say something as a footnote here about the
15 agreement. Where you get Kappa with a large
16 agreement, or the expected number very large,
17 producing a small value Kappa, is where the numbers
18 are concentrated on that main diagonal in just one
19 cell. So that you see for the low-risk, where you
20 have 90 cases, 89 of them are down there in that lower
21 righthand corner. That is the kind of thing that
22 gives you a large expected number and a small Kappa.

23 So when you get to the next level of
24 prevalence, the intermediate risk, you see there's a
25 much more even distribution of cases between those two

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1 cells, and that that sort of lightens you up a little
2 bit on the expected number. Then when you get to the
3 high-risk group, it begins to fall off again because
4 you've got numbers that are concentrated up in that
5 upper lefthand corner.

6 All of the agreement indices show a
7 pattern with prevalence. What I am going to suggest
8 is the one that we might consider as my basic analysis
9 of agreement between QFT and TST is the overall
10 agreement, simply because it shows the least variation
11 with prevalence.

12 Next slide, please. What I have done here
13 is to calculate the overall agreement for the three
14 risk groups and calculated the confidence intervals.
15 I want to call your attention to the lower confidence
16 limit, because that's what we like to say is what we
17 know for sure, that the agreement is going to be
18 possibly that low, but it may also be higher.

19 So for the low and intermediate group
20 we've got 80 percent or more agreement in terms of the
21 lower confidence limit. So I would say that basically
22 is telling me what the chances are of agreement
23 between QFT and TST for the suspected group. It falls
24 off and the agreement is down around two-thirds. If
25 you are a user of the McNemar test, I would also say

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1 that we have significant McNemars in the suspected
2 group. It tends not to support agreement at that
3 level, but it is okay at the low and intermediate
4 levels.

5 Thanks for your attention.

6 CHAIRMAN WILSON: Thank you.

7 At this time I would like to invite the
8 panel members to ask questions of the FDA's speakers.

9 Dr. Charache?

10 DR. CHARACHE: I wonder if I could ask a
11 question of Mr. Dawson. Looking at the percent
12 agreement, if we go back to your next-to-last slide
13 for a moment, I think maybe it is the one before it.

14 MR. DAWSON: No. 7?

15 DR. CHARACHE: No, it's the complicated
16 one, No. 6. If we look at, instead of the overall
17 agreement, which is the first three columns, if we
18 look at the agreement, just the agreement with the
19 TST-positive and negative, there the agreement is very
20 good for the negatives, but only 12 percent agreement
21 among the positives.

22 MR. DAWSON: In the low risk, yes.

23 DR. CHARACHE: In the low risk. Now
24 looking at the WRAIR, it is also 12 percent for the
25 low-risk group, and that's the group that we're

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1 targeting. So I'm wondering if, rather than looking
2 at the overall agreement, which certainly in low-risk
3 patients and moderate-risk patients who are the ones
4 where we are really looking for latency in, the
5 important question is agreement of the positives, not
6 the negatives. There will always be more negatives.
7 If we use the overall agreement, we will always see
8 very good agreement, but the group we are concerned
9 about are those who are candidates for therapy.

10 So I wondered if we could look at that
11 number for the populations for which the test is
12 proposed; namely, those for which there is a test of
13 latency, and just look at the agreement of the
14 positives, the candidates for therapy, which is the
15 purpose of the test. Because it seems to me that for
16 most tests we either want to look at the negative
17 agreement or the positive agreement, and for this test
18 we want to look at the positive agreement, which in
19 the candidate populations for therapy are going to be
20 in the low-risk category, where agreement is extremely
21 poor.

22 Then we have to decide what to do with it.

23 Maybe it is to increase the agreement by modifying
24 the cutoffs. But I wondered what the comments would
25 be on that thought.

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1 MR. DAWSON: I think it is appropriate to
2 look at agreement with the positive TST results as
3 long as you keep the prevalence groupings broken out,
4 because it is drastically different.

5 DR. CHARACHE: Yes, I would make the
6 prevalence grouping the candidate population for which
7 the test is targeted.

8 MR. DAWSON: Are you saying that there is
9 one part or another of this table right here that we
10 are looking at that would be appropriate for that
11 interpretation?

12 DR. CHARACHE: Well, the low-risk group
13 would. That's not a candidate for skin testing now,
14 according to CDC, because of false positives. But the
15 false positives under that category would be fair
16 greater with the QFT test.

17 So I would want to look for the
18 concordance with that population as opposed to
19 negatives which will always overwhelm your ability to
20 know about the group you want to treat when you're
21 looking at the targeted population.

22 CHAIRMAN WILSON: Dr. Cockerill?

23 DR. COCKERILL: Another question regarding
24 statistics: Of course, the negative 99 percent, as
25 you mentioned, is not that remarkable considering it

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1 is a very low prevalence group. So you are going to
2 have a very high percent there because the prevalence
3 is so low.

4 Do you have any idea -- we saw some two-
5 by-two's I think earlier -- if the cutoff is 30
6 percent versus 15 percent, how that would affect that
7 positive 12 percent result, or can you make any
8 comments about that?

9 MR. DAWSON: I don't have any intuition
10 about that. We did see that when they raised the
11 cutoff for percent human response from 15 to 30, that
12 the specificity went from 90 up to 98. So it is
13 possible here and now, after the fact, to go through
14 and look at the different cutoffs, which the company
15 has been doing. We encourage them to do that because
16 you want to learn from the PMA studies as well as to
17 get an approval.

18 We do have analytical means after the
19 fact, a type of cross-validation involving what's
20 known as the bootstrap to validate a different cutoff
21 after the fact, using the clinical trial data. But
22 I'm sorry, I don't have just off the top of my head
23 any idea what that would do for agreement.

24 CHAIRMAN WILSON: Dr. Janosky?

25 DR. JANOSKY: The question is either for

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1 Mr. Dawson or Dr. Sacks. I want to go back a few
2 levels, sort of thinking about the data and analyzing
3 the data for a second. The sponsor had told us this
4 morning that the values of test performance for the
5 TST are quite low. If we use that as an assumption
6 and we work from that, when we see discordance with
7 these two tests, do we have any hint as to what might
8 be going on?

9 I ask you, when you answer that, to please
10 think about the fact that the odds ratio for the Asian
11 population that the sponsor reports is about a 5, and
12 the odds ratios for some of these other personal
13 characteristic variables are quite high in the
14 discordance.

15 MR. DAWSON: I don't have any analysis to
16 offer on the discordance. Sorry.

17 DR. JANOSKY: Okay. I am still trying to
18 tease apart as to, if we're trying to evaluate this
19 test based on an imperfect test, who are we penalizing
20 when we come up with disagreements? I mean, just
21 think of some ways to sort of try to answer and think
22 through the question, but since you two are very close
23 to the data, I was wondering if either one of you had
24 worked through some of those hypotheses.

25 MR. DAWSON: If Leonard doesn't have an

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1 answer, it may be that the company does because the
2 company always knows the data better than any of us at
3 FDA.

4 (Laughter.)

5 DR. JANOSKY: Well, I would feel
6 comfortable also asking the question for the sponsor.

7 DR. SACKS: This is nothing really new,
8 but I think the other way in which a clinician would
9 look at the data is in terms of the TB risk.
10 Obviously, in a population where the risk is
11 negligible one would like to see the lowest positive
12 rate; in a population where the TB risk is highest,
13 one would like to see the highest possible rate,
14 bearing in mind the caveats for the different types of
15 tastes.

16 DR. JANOSKY: Yes. When I took a look at
17 one of the tables that you presented today, which I
18 thought was very illuminating, by the way, the one
19 where you were looking at the different populations
20 and the expected prevalence rates in both of those
21 tests, if I think about it from a population
22 perspective, my conclusions of those tests might be
23 that I'm very comfortable with it. If I think about
24 it on an individual basis, that is what I am trying to
25 grapple with because that's really where we are.

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1 DR. SACKS: Yes, I think, as we get down
2 to the level of the individual, not only are the
3 overall prevalences of positive tests in each
4 population group important, but the concordance within
5 those, and that's what I tried to highlight with the
6 Venn diagrams.

7 Personally, I am not sure how in those
8 groups one does interpret discordant results, a
9 positive QFT with a negative TST, or a positive TST
10 with a negative QFT. You know, all I can say is that
11 with a TST, with all its pitfalls, at least it has
12 some clinical validation over the many years of use.
13 We know the percentage of patients who are going to
14 get TB, if we found a positive TST. We know that TST
15 is likely to convert if patients have been exposed to
16 TB. So we have some sense of how the TST behaves
17 clinically, but I'm not quite sure how to evaluate the
18 QuantiFERON.

19 DR. JANOSKY: So, in that respect, you are
20 more comfortable sort of putting the onus on the new
21 test as opposed to the TST, just because of the
22 performance and the current approval? Is that what
23 you are concluding?

24 DR. SACKS: Well, in the absence of data,
25 I think what we would have to do, the way I would

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1 phrase it is we would need to see data to validate the
2 discordant results by QFT.

3 DR. JANOSKY: Okay. Then that goes to the
4 question that I asked. Is there any information
5 available besides seeing some of the discordant
6 personal characteristics data that were presented in
7 the application?

8 DR. SACKS: I will defer to the company
9 there. I don't have any additional data.

10 CHAIRMAN WILSON: Would anyone from the
11 sponsor like to comment on that?

12 DR. RADFORD: First, I will deal with the
13 issue in the low-risk group, which we're actually
14 stressing here because it is the one with the 12
15 percent.

16 The thing that we would actually like to
17 make absolutely clear here is that this is an
18 extremely low-risk group. This is a group that has
19 been deleted on every risk factor that we can find. I
20 would note that the FDA noted that there, in fact, in
21 the initial classification we actually had to go back
22 and delete out people who were set perhaps initially.

23 No acquired risk. There is no risk.

24 So they are at absolutely no risk and put
25 there because there is no reason to believe that any

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1 of them have tuberculosis whatsoever. So the point we
2 make there is that we are not really looking at that
3 data for concordance. We're looking at what you might
4 call the random or the background variation of either
5 test. Given that point, that is why we stress the 30
6 percent is a more effective cutoff in a very low-risk
7 group because you don't want to show up in low-risk
8 groups a large number of individuals.

9 I can answer the two-by-two table at the
10 30 percent margin by saying, in fact, there is no
11 concordance. We actually have no double positives and
12 we have two individually positive for the TST and to
13 QuantiFERON at the 37 group, and the rest of them are
14 the negatives.

15 But I think that is the point that we
16 would like to stress: that if you actually start
17 focusing in on the low-risk groups, the WRAIR one
18 group, the CDC one group, you are looking at a group
19 that is stressed to have no contacts, no possible
20 exposure to anyone with TB, nothing. In fact, you
21 will notice in the WRAIR group we even took out people
22 from an incidence of greater than 10 in 100,000 states
23 of the United States. Now that is a very severe
24 cutback. So we don't expect great concordance in
25 that. Of course, it is a low incidence group, and of

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1 course the cutoff will be low, as discussed.

2 So I don't think we should actually focus
3 in on concordance in low-risk groups because basically
4 none of these people probably have tuberculosis. That
5 is why we say we should raise it up to 30 percent, in
6 our case to get that specificity.

7 CHAIRMAN WILSON: Dr. Charache?

8 DR. CHARACHE: The concordance is also
9 extremely low. It is not 12 percent. I didn't do the
10 calculation, but it is maybe 15 percent in the
11 secondary risk group at WRAIR. Those two groups, one
12 and two, were added for analysis as being those that
13 were candidates for the test.

14 DR. RADFORD: Perhaps I'll might this
15 point clearly: In the ATS and the CDC guidelines, it
16 doesn't say: Test people at no risk for tuberculosis.

17 It says: Don't test people with TST with no risk for
18 tuberculosis, but if you must, use the 15-ml cutoff.
19 Low-risk people aren't generally recommended to be
20 tested. The people who are recommended to be tested
21 are those at some risk of latent tuberculosis
22 detection.

23 The WRAIR two group, again, is in fact a
24 fairly limited risk there because they're the group
25 that's actually incorporated -- the only risk factor

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1 incorporated is they came from a U.S. state with
2 greater than 10 cases of TB per 100,000.

3 Jim, would you like to speak to that?

4 DR. ROTHEL: Yes, if I could just -- we
5 are not proposing to use the 15 percent cutoff for
6 low-risk people. We are proposing to use the 30
7 percent. So in both of the low-risk groups from the
8 WRAIR study, specificity is not yet equivalent to the
9 TST.

10 But I want to come back to your
11 discordance question because I don't know if we
12 totally addressed what you were asking.

13 DR. JANOSKY: You didn't, so thank you.

14 DR. ROTHEL: I think it is terribly
15 difficult to try and resolve what the real result is
16 in human studies. They're going to be very long-term
17 studies. They're going to take us a long time to do,
18 confounded by the fact that if you identify an
19 individual as being positive in a test, you may have
20 to prophylaxis them. So, therefore, the possibility
21 of their coming down with disease is vastly reduced.

22 So it is basically an ethically difficult
23 study to do and a very long-term study. I think the
24 best evidence comes from the bovine data, where we can
25 actually kill the animals and we have a gold standard,

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1 or that is about the only conclusion we can draw
2 within getting into terribly complicated, long-term
3 studies that we probably wouldn't be able to ethically
4 do.

5 CHAIRMAN WILSON: We have time for one
6 more question. Mr. Reynolds?

7 MR. REYNOLDS: On the retesting of the
8 discordant results, does anyone know how close the
9 initial result was to the cutoff? Anyone from the
10 manufacturer have any idea whether those discordant
11 results have changed on retest, how close they were to
12 the cutoff?

13 DR. JOLLY: If I might be allowed to
14 address that question, Mr. Chairman?

15 CHAIRMAN WILSON: Yes.

16 DR. JOLLY: I can't give you quantitative
17 answers. I can tell you that almost all of the
18 changes were very close to the cutoff. I think this
19 is a characteristic which is inherent in any test
20 where we are trying to find a magic number. I think
21 the strength of any quantitative test -- and this
22 includes the TST as well as the QFT -- is that there
23 is an underlying numeric quantity which allows us to
24 alter the cutoff appropriate to this.

25 Thank you.

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1 DR. NOLTE: Can I get a clarification on
2 the retesting? For the QFT, that was a second sample
3 drawn at another point in time? Or? Clearly, the
4 skin test was.

5 DR. ROTHEL: Yes, I think Jerry Mazurek
6 who is here from the CDC might be able to address that
7 accurately, but from my memory anyone with a
8 discordant result in the CDC study was meant to have
9 another blood drawn within two months. Yes, Jerry?
10 Yes. Thank you, Jerry. Retested, a very small
11 percentage of those individuals that had discordant
12 results were done. Some were retested as soon as a
13 week after, and the others were tested up to a month
14 after the initial test.

15 CHAIRMAN WILSON: Thank you.

16 At this point I would like to move to the
17 open public hearing.

18 Two individuals have notified the FDA that
19 they would make a public comment. The first is Dr.
20 James McAuley from Cook County Jail, Illinois, who is
21 going to discuss difficulties with tuberculosis
22 testing.

23 DR. MCAULEY: Thank you. My name is Jim
24 McAuley. I'm the Medical Director at Cermak, which is
25 Cook County Jail, one of the larger jails in the

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1 country. I have done TB control for about 10 years.
2 I will make it very brief. I will just give you a
3 quick overview of how we use it.

4 I do a lot of actually teaching on
5 tuberculosis. I will say that when I teach, I always
6 say that if you're going to use 15 millimeters, you
7 shouldn't have done the test. I mean, that's really
8 functionally how I think of it. I have always worked
9 in high-risk groups. So, for me, when I talk, think
10 of my population as being right in the middle.

11 I would also say that clinically I am very
12 much a clinician in this regard: I don't use it at
13 the other end either. If they clinically have
14 tuberculosis, I don't use the skin test. I use my
15 clinical and my laboratory. If they have a smear-
16 positive, I see what that organism is.

17 Prisons and jails are an important
18 environment because there are 2 million people behind
19 bars in the United States with 600,000 in jails.
20 Jails are pre-trial detection centers. So you're
21 awaiting trial, or if you have been incarcerated for
22 less than a year. Prisons are where you go for a
23 longer period of time.

24 This is a high-risk group. This is a
25 group that is a targeted testing group by the CDC's

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1 LTBI guidelines. Six million people pass through our
2 correctional system each year, so a large segment of
3 our population. It is mostly individuals who are high
4 risk for tuberculosis.

5 It has been growing, so I think it is a
6 population base that needs to be addressed from a
7 public health point of view. This just gives you a
8 sense.

9 Now, again, I work in a jail setting,
10 which is a passthrough population. In our setting the
11 majority are non-white and usually of lower
12 socioeconomic status.

13 Again, I am going to go quickly because I
14 just want to give you a flavor of what environment we
15 practice in and then how we use the TB test. We have
16 a lot of public health issues we address. The one we
17 are obviously focusing on is tuberculosis, but there
18 is a lot of HIV and AIDS in the correctional system.
19 In our jail setting 2.5 percent are HIV-infected, but
20 in New York it has been as high as 15 to 20 percent in
21 serosurveys in their jail system. We also have a
22 great deal of hepatitis C.

23 It is a congregate setting. So there are
24 studies that I will show you real briefly in a second
25 that show that jails amplify tuberculosis transmission

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1 in the community. In fact, I will mention it now, but
2 in Tennessee 42 percent of their active tuberculosis
3 had passed through the jail system in the preceding
4 year. So they speculate that their jail was actually
5 the transmission foci. In New York active
6 tuberculosis, one of the independent risk factors for
7 developing active TB in New York City is having spent
8 time in the correctional setting. Again, the case
9 rates for active disease are much higher.

10 So within that setting we have a fair bit
11 of active disease. Now we want to target, as our
12 cases go down in the U.S., we are really focusing on
13 what to do with LTBI, or latent TB infection. So that
14 is really the focus population.

15 Again, I don't think either of these
16 tests, to my clinical judgment, are that important for
17 active disease. We use chest x-rays. We use
18 symptoms. We use all of that to determine active
19 tuberculosis, but what we ask ourselves is: Can we
20 identify people who pass through a correctional
21 setting who are at high risk for tuberculosis and can
22 we get them treatment for their LTBI, so that they do
23 not develop tuberculosis down the road? That has been
24 our big focus at our site.

25 Some of the references you have of the

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1 publications that discuss tuberculosis in prisons and
2 jails, and, again, this is the Tennessee study, which
3 basically said that it was very important.

4 I want to get to the -- maybe I will pass
5 through the immigrants, because I am looking at the
6 time and I know that there are people needing to go
7 on. Again, I want to get to just what we are focusing
8 on here, screening of this high-risk population.

9 We do also screen employees. So there are
10 two ways in which we look for tuberculosis in our
11 setting. The CDC says that we should have basically
12 an appropriate policy. I also think it is very
13 important to keep in mind that a jail in Chicago is
14 not the same as a jail in Montana as far as TB goes.
15 So in a jail in Montana you might not do either test.
16 Always keep that in mind.

17 So all TB is local, and I think it is
18 interesting to hear this discussion of 10 cases per
19 100,000 being the high risk. If you are from
20 Illinois, where we are one of the high rate states,
21 comparable to most of your southeastern states, if you
22 are outside the metropolitan Chicago, your case rates
23 of TB are about 2 per 100,000. So you are actually a
24 low risk. So if you are a military recruit from rural
25 Illinois, you're obviously a low-risk person, very low

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1 risk, but you would have been lumped into high risk.
2 Conversely, the alternate would happen if you were
3 from an urban center that was diluted by a rural
4 population -- basically, the imperfections of all this
5 epidemiology.

6 So at our site we screen 100,000 detainees
7 a year. That's our passthrough population. On any
8 given day, 10,500 detainees live on a 100-acre campus.

9 So we have both geography, a large compound to deal
10 with, and volume, 250 to 300 individuals passing
11 through on a given day.

12 When you pass through our system, we
13 screen you medically and we look for mental illness,
14 and we do a mini-chest x-ray because active disease is
15 the thing we are worried about from a transmission
16 point of view. We do place a skin test. Frankly, I
17 wonder if I want to place a skin test. I think it is
18 an important public health service, but it is not very
19 important for my institution, if you think about it,
20 because I really need to just look for active disease.

21 I will show you some data in a minute about why I
22 wonder about whether we should place a skin test.

23 But having said that, many, if not most,
24 states' regulations require correctional facilities to
25 place skin tests because it has been entrenched as one

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1 of the things you ought to do to look for tuberculosis
2 in a jail setting. So whether or not I believe it is
3 scientifically valid or valid for the individual
4 patient, I am required to place it.

5 So we place 250 to 300 tests over a few
6 hours every day, and we try to read them at 48 to 72
7 hours. We successfully read between 25 and 30 percent
8 of those skin tests. So 75 percent of the skin tests
9 we place are not read.

10 We do a mini-chest x-ray, which is read
11 within 12 to 16 hours. We read all of those,
12 obviously. This is how you do it: You take the 100
13 millimeters, you blow it up; you look for
14 tuberculosis.

15 We have found over the years that,
16 fortunately, our TB case rates are going down. We
17 find most of our cases by chest x-ray, but we do have
18 some people who come in with a normal chest x-ray but
19 give us symptoms that suggest tuberculosis.

20 As you would expect, our tuberculosis case
21 rates mirror the city a little bit. We believe we
22 have actually significantly contributed to the city's
23 control of tuberculosis because, as an example, 60
24 percent of people who are homeless in Chicago pass
25 through the jail each year. So we actually probably

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1 control a lot of the homeless tuberculosis
2 inadvertently. So we contribute significantly.

3 Now to the case in point, where I think
4 that skin tests or any blood test is important.
5 Actually, I should take a second -- I didn't explain.

6 I have had nothing to do with the company except they
7 heard my presentation at a TB meeting earlier this
8 year and asked if I would come. So they have paid my
9 way here and for my time today.

10 So I say that because, obviously, I have
11 been paid by them and they have paid my
12 transportation, but my personal view is I would like
13 to have a good test. I actually don't really care who
14 gives me the good test, but I would like to have a
15 good test.

16 We started looking at LTBI because we have
17 this problem that we are placing 100,000 skin tests,
18 25,000 are being read. Then we started them
19 Isoniazid, and only 11 percent completed because they
20 pass through our jail so quickly. So we felt it was
21 somewhat of a futile activity.

22 So we began using the two-month rifampin
23 pyrimidazide, and we got our completion rates up to 67
24 percent. So now I think we are actually doing a good
25 service for the community and for the individual

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1 patient, because not only can we identify them with
2 infections, some of them, but we can get them on
3 therapy and actually complete therapy. So now we are
4 a little bit more excited about our latent TB program.

5 But what are our big challenges left?
6 Well, our biggest challenges is this graph, which is
7 probably better in your handout than on the screen.
8 The next one will show it as well.

9 That is, when you come to jail, the good
10 news is you get out right away. The bad news is I
11 don't have time to intervene in your health care very
12 well. What this translates into practically speaking
13 is that, as seen on the very last slide, fully 22
14 percent of people are gone in 48 hours. So 22 percent
15 of the skin tests I have no chance of reading, and
16 then the rest trickle out over time, but then I have
17 the logistics of staffing going to find these people
18 over a 100-acre compound who have been moved around
19 for security reasons, not for medical reasons. That
20 is the other reason why we can't read the skin tests.

21 So from my point of view, when a person
22 enters, if I draw their blood, which I do already
23 looking for syphilis, because we play a big role in
24 the city's syphilis elimination program, I could at
25 least identify those who are positive. Now can I

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1 engage them and complete them in treatment? I think I
2 can complete more of them than I used to because I am
3 completing about two-thirds now. How many more I
4 don't know, but from my point of view it would be
5 significantly improved if I could actually identify
6 quickly, without having to bring that person back.

7 I think it gets to the point about, if
8 somebody doesn't come back for the reading, doesn't
9 that mean that they are not likely to finish their
10 therapy, which is what I think is inherent in the
11 question. I think in our population what it means is
12 we are just not able to get to them to read it. Now,
13 again, we may not complete all of them because of them
14 will go again.

15 So from my point of view, in a
16 correctional setting a test that at least performs
17 comparable to the current in that intermediate group,
18 which I think is the right group to apply any test,
19 would be of some value to us.

20 Thank you.

21 CHAIRMAN WILSON: Thank you, Dr. McAuley.

22 The second public comment will be given by
23 Mr. Reynolds. I would like to note that Mr. Reynolds
24 is prepared and is giving his statement from the State
25 Department of Health Laboratory in Pennsylvania.

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1 MR. REYNOLDS: This statement is actually
2 from Mr. William Barry, who is the Director of the TB
3 Control Program for the Commonwealth of Pennsylvania.

4 I will make it very brief.

5 Thanks for the opportunity to comment on
6 the QuantiFERON TB test. Our hope is that the test
7 will be very useful in the diagnosis of latent
8 tuberculosis infections and would be more accurate
9 than the reported 25 percent false negative rate in
10 some PPD studies.

11 Our problems with the PPD include ensuring
12 trained staff, placing and reading the test with
13 accuracy and consistency, patients returning within 48
14 to 72 hours after the test is administered for
15 reading, and difficulty in separating the true latent
16 tuberculosis infection from positive PPD's due to BCG
17 or non-tuberculosis mycobacterial infections.

18 Hopefully, these problems could be
19 resolved with an ELISA test. On a practical level,
20 would the test be able to be performed by laboratories
21 across Pennsylvania or just the Bureau of
22 Laboratories? This would be important to us in the
23 rapidity of specimen submission and obtaining results.

24 My understanding is that JAMA will have a
25 report on the QFT test this week. We're looking

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1 forward to reviewing it.

2 I hope this is of some help to you.
3 Again, thanks for the opportunity to comment. Any
4 questions, please give me a call. Thank you.

5 CHAIRMAN WILSON: Thank you.

6 Does any other member of the audience want
7 to make a statement?

8 (No response.)

9 If not, the open public hearing session is
10 now closed.

11 We would like to take our lunch break now.

12 We will reconvene promptly at one o'clock.

13 Thank you.

14 (Whereupon, at 12:16 p.m., the proceedings
15 recessed for lunch, to reconvene at 1:00 p.m. the same
16 day.)

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

1:07 p.m.

CHAIRMAN WILSON: All right, I would like to reconvene the meeting at this time.

This is the open committee discussion portion of the meeting. This portion of the meeting is open to public observers. However, public observers may not participate except at the specific request of the Chair.

We have two primary reviewers for this PMA submission, neither of whom would like to make individual comments. Therefore, I would like the FDA to put up the first question for the panel.

Okay, the first question states: "Did the data from the two U.S. studies provide sufficient information on the performance of the QuantiFERON-TB assay, and are there other types of data or other types of analysis that can supplement those studies?"

So I would like the members of the panel to make any comments regarding those two questions. Dr. Charache?

DR. CHARACHE: The CDC paper emphasized that one of the significant variables that were found on multivariate analysis was the differences between the five sites that did the studies. Apparently, the

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1 patients were the same, but there were differences. I
2 wonder about looking at the two-by-two comparative
3 data from each site and then see if we can understand
4 the differences between sites.

5 Similarly, I would wonder about looking at
6 some of the differences, see if we can understand
7 better the differences between gender and age. I am
8 thinking here whether this is the kind of test that
9 would use different breakpoints by gender or by age
10 rather than a single one for all comers.

11 I think it would be very helpful to look
12 at the data for all of the groups, not in terms of the
13 overall agreement, but in terms of the population at
14 risk and the purpose of doing the test in a given
15 population to determine which variables should be
16 addressed.

17 CHAIRMAN WILSON: Does the sponsor have
18 the data divided in those ways, in a way that you
19 could present it now?

20 DR. JOLLY: Mr. Chairman and Dr. Charache,
21 if I can direct your attention to page 2-189, volume
22 2, page 189, in this report we compare one measure of
23 agreement between sites in the CDC dataset and also
24 between risk strata in the same dataset.

25 Now I will mention here that the fact is

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1 these tables are Kappa statistics which, as the FDA
2 statistician pointed out, is a measure which is, if
3 anything, biased toward low agreement status, because
4 in the low population groups we chose this measure
5 specifically because it did not give any implication
6 of high value. The Kappa statistic is bias toward low
7 values and low prevalence populations. This is why we
8 chose this statistic.

9 Now if you look at the first table on page
10 189 of volume 2, you will see that we have got
11 measures of Kappa broken down by each of the five
12 different sites. All the values there are uniform.
13 There's no particular variation between the sites and
14 the agreement or disagreement status, whereas, as has
15 been pointed out by the FDA statistician, there are
16 differences, as one would expect, between the
17 different risk groups because Kappa does depend upon
18 the prevalence in the data.

19 I will also point out that on the page
20 after that there are the same figures broken down by
21 site within this group. So we get comprehensive
22 breakdown there, Mr. Chairman, of the measures of
23 agreement by site.

24 DR. CHARACHE: Yes, I think what I was
25 referring to, again, was not the overall agreement. I

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1 think Dr. Sacks pointed out that we have to know the
2 relationships between what the overlapping agreement
3 is and how they differ. I was thinking in terms of
4 table 5, the factors associated with negative
5 tuberculin tests and the positive interferon gamma
6 from the CDC paper in which it did vary by location.

7 DR. JOLLY: This is the JAMA paper?

8 CHAIRMAN WILSON: Yes.

9 DR. JOLLY: Yes. Jim, do you have a copy
10 of that?

11 DR. ROTHEL: Thanks. I just got this, and
12 I copied this, and it looks quite nice.

13 The only comment I would like to make is
14 that, as far as my reading of the paper and my
15 understanding of the data -- and I wish Jerry Mazurek
16 was here, who actually did the study -- but the
17 discordance associated with different sites is
18 associated with the TST. It wasn't associated with
19 QuantiFERON. It was associated with people -- did
20 give preference, which are just two of the thoughts
21 from memory.

22 DR. CHARACHE: I was just saying I think
23 this probably would be helpful to look at, and I think
24 might be helpful to look at with the two-by-two tables
25 and see how the sites compared with each other.

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1 DR. ROTHEL: For the individual sites.

2 DR. CHARACHE: Yes.

3 DR. ROTHEL: I understand. That is a good
4 comment. I don't believe it is in your panel pack.
5 The only trouble is that in some sorts there are as
6 few as 15 or so people in group one, for example. The
7 two-by-two table is very meaningless with the low
8 numbers, but, yes, we can provide that if you need it
9 at a later date.

10 CHAIRMAN WILSON: Dr. Baron?

11 DR. BARON: The only other information
12 that I think would be helpful, which you don't have,
13 and I fully appreciate the difficulty of gathering
14 those data, are the results of your assay and skin
15 tests in patients who are infected with pulmonary
16 disease of mycobacterium other than tuberculosis.

17 CHAIRMAN WILSON: Dr. Charache?

18 DR. CHARACHE: That reminds me of another
19 question, which has to do with the validity of the M.
20 avium as an overall control for all mycobacteria other
21 than tuberculosis. I think particularly in the cattle
22 studies I would wonder about the mycobacteria that are
23 found in the ruminant sacks of the cows.

24 I am wondering, if you had somebody with
25 kansasii and you tested with the assay, whether the M.

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1 avium would be an adequate control or not. Or, if you
2 just did the study that you did that showed that M.
3 avium control was a very good one, where you looked at
4 the ability of the M. avium to modify the results of
5 the PPD, if some of these false positives you could do
6 the same thing, but instead of using M. avium, use a
7 different mycobacteria. I'm just interested in
8 knowing whether we could extend the control if,
9 instead of just M. avium as a control, there were
10 other mycobacteria that are common causes of human
11 disease included as part of the control. I think the
12 control idea is terrific, however.

13 CHAIRMAN WILSON: Yes, go ahead.

14 DR. WOOD: Maybe I can just comment from
15 the veterinarian point before it over to other people
16 to comment on the human. M. avium is actually used
17 worldwide as the distinguisher for comparative
18 testing, probably mostly initially because it was a
19 fast-growing organism and you could make the PPD.
20 But, in practice, it is actually an extremely good
21 antigen to us, as demonstrated by its extensive use.

22 Obviously, we made a decision in
23 converting to new tests just to stick with the same
24 antigens. The only other antigen that we have
25 extensively looked at in the cattle is Joni's disease

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1 and using impaired tuberculosis antigens. It answers,
2 I think, the question raised earlier: In the long run
3 would this sort of technology work with MOTT
4 infections? It is working quite well in that
5 circumstance.

6 So I think you could possibly use other
7 PPD's, but I think in general practice is showing us
8 that M. avium is a pretty good indicator, although not
9 absolute, like anything in these assay systems.

10 DR. CATANZARO: I wanted to remind us of
11 the work that was done by the Navy when they look at
12 the various tuberculins from rapid growers, from
13 yellow bacillus, kansasii, PPDB, and from the radish,
14 the scraphilacio. That work was done in skin testing.

15 From that came the concept that PPDB from the battey
16 bacillus or avium was used as a representative of
17 other mycobacteria. That has been pretty well
18 established in skin testing.

19 Obviously, it hasn't been looked at by
20 QuantiFERON. But I think that rather than looking at
21 it as a reflection of avium infection, we should look
22 at the response to avium as representative of other
23 mycobacteria.

24 DR. CHARACHE: Thank you.

25 CHAIRMAN WILSON: Dr. Nolte?

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1 DR. NOLTE: I know the intended use of
2 this assay is not, the way you have stated it, is not
3 to include HIV-infected patients, but, clearly, the
4 test is going to be used in those populations, either
5 knowingly or unknowingly.

6 I am wondering, there was data presented,
7 published data presented in the packet that, at least
8 to me, indicated that the test performance, at least
9 agreement with the tuberculin skin test was really not
10 that much different with HIV-infected individuals as
11 it was with uninfected individuals. Is there any way
12 that more data like that could be included in terms of
13 the submission?

14 DR. ROTHEL: Yes, I agree, we have a fair
15 bit of data on HIV-infected people in here. There is
16 a paper by Converse, et al., Quatamera, et al., and
17 the Mason study that the abstract's reported in your
18 panel pack.

19 The truth of the matter is we don't
20 believe we have sufficient data to go to the FDA to
21 get approval for it. It is something that we may do
22 as a post-market study to extend their claims in HIV-
23 infected individuals, but it is not a simple study to
24 do and quite an expensive study to do.

25 DR. NOLTE: I understand.

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1 DR. ROTHEL: Yes.

2 DR. NOLTE: The other thing that is of
3 concern to me is the intended use. The package insert
4 that you folks included was a little confusing to me.

5 In one place it said, essentially, to be used as an
6 aid in detection of infections with MTB, and in
7 another place in the package insert it said it is an
8 aid in detecting latent TB infections. I am not sure
9 -- I mean there is not a lot of data that you
10 presented in terms of the performance of this test in
11 active disease.

12 So I guess, where are we going with the
13 intended use here?

14 DR. ROTHEL: The intended use is not meant
15 to have the "latent" in there. That was a
16 typographical error.

17 We see no reason why not to include it for
18 TB in general. When you are screening individuals for
19 latent TB infection, you are invariably going to pop
20 up very random, a very seldom event of someone with
21 active TB. We have sufficient data, we believe, to
22 prove that or to demonstrate that individuals with
23 active TB disease are detected by the test in the vast
24 majority.

25 DR. NOLTE: Again, in the data that is

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1 included as part of this submission, how many infected
2 patients are --

3 DR. ROTHEL: There were 54 in there, and
4 the other data we provided in support was 129 from
5 that Australian study.

6 DR. NOLTE: So we're talking about a total
7 of 200 or so?

8 DR. ROTHEL: Nearly 200 or so, yes.

9 DR. NOLTE: Actively-infected individuals?

10 DR. ROTHEL: Yes, and both studies have
11 come out with a sensitivity of 81 percent. It's not
12 perfect, but --

13 DR. NOLTE: Sure.

14 DR. ROTHEL: -- it does definitely have
15 utility for detecting active TB disease.

16 DR. NOLTE: Okay, thank you.

17 CHAIRMAN WILSON: Dr. Carroll?

18 DR. CARROLL: Yes, along those same lines,
19 could the sponsor then clarify in terms of the
20 labeling whether you will then seek approval for both
21 cutoffs, the 30 percent cutoff for the low-risk
22 individual and the 15 percent cutoff for the
23 intermediate? Is that what we're talking about here?

24 DR. ROTHEL: Yes, that's exactly what
25 we're asserting, yes.

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1 CHAIRMAN WILSON: Dr. Durack?

2 DR. DURACK: With regard to the question
3 about supplementary data, I'm sure that it's clear
4 from the discussion that the pediatric group is
5 particularly important, and I know you will be working
6 on that. I would personally put that as the first
7 priority as far as supplementary data, and I would
8 make the additional point that this could be a group
9 where it may be important to separate the older
10 children from the younger children, possibly even
11 infants, younger children, and teenagers. So I think
12 it might be better not to just lump everything as zero
13 to 18 for that study.

14 CHAIRMAN WILSON: Okay. Dr. Beavis?

15 DR. BEAVIS: My hope, too, is as
16 additional data is being collected that
17 reproducibility be looked at, not repeating a
18 specimen, you know, different time from the same
19 patient, but splitting the specimens and testing them
20 in different laboratories.

21 CHAIRMAN WILSON: Any other comments on
22 the first question?

23 (No response.)

24 Okay, if we could have the second question
25 then?

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1 The second question states: "Testing of
2 control material is not available to compare results
3 between sites in the clinical studies. Are the
4 manufacturer's procedural and specimen controls
5 adequate to ensure reliability and reproducibility of
6 QFT testing between laboratories?"

7 Any comments or questions from the panel?

8 Dr. Nolte?

9 DR. NOLTE: If I remember correctly, the
10 only data that we saw was the data that Ms. Shively
11 presented that was new, I mean that wasn't part of the
12 packet in terms of the two laboratories' split sample
13 analysis. Am I correct?

14 MS. SHIVELY: That was in your packet.

15 DR. NOLTE: That was in the packet?
16 That's the only data available in terms of
17 interlaboratory reproducibility?

18 DR. ROTHEL: The full study, yes.

19 DR. NOLTE: Okay. Like I suggested,
20 that's probably not enough.

21 CHAIRMAN WILSON: Dr. Charache.

22 DR. CHARACHE: I think the studies of
23 interlaboratory reproducibility would go a long way in
24 knowing about the ruggedness of the test, and I think
25 there are some questions about the ruggedness of the

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1 test, if in fact there are differences between the
2 labs. I think this would be very helpful to us to
3 establish that, and then you could determine the
4 extent to which you needed outside controls.

5 I'm obviously concerned about the false
6 positives because of the therapeutic implications in
7 the low-risk populations.

8 DR. LEWINSOHN: What would an outside
9 control be?

10 DR. CHARACHE: I'm not sure what the
11 outside control would be. That is why I am hoping we
12 won't need them.

13 DR. LEWINSOHN: I'm sort of struggling
14 with that, I guess, because it seems like your
15 standard curve sort of is the control in a way, I mean
16 unless you're going to ship serum from -- or not --
17 well, I guess it is serum -- from these assays or it's
18 actually I guess plasma, from other assays as a
19 control.

20 DR. CHARACHE: Yes, I suppose a surrogate,
21 at least interferon that you should get within a given
22 range in your system if the conditions are right.
23 It's not perfect. It doesn't start with a leukocyte,
24 but you're in better shape.

25 CHAIRMAN WILSON: If there's a suggestion,

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1 a recommendation to the sponsor that they provide
2 additional data on this, the question would be: How
3 much data would suffice?

4 DR. NOLTE: Well, I mean, basically, I'm
5 trying to remember the data that we have in front of
6 us, but it's two sites and 50 specimens, right? --
7 almost all of which were positive. I think one of the
8 points that came out in terms of this was the sort of
9 reproducibility of negative as well. So certainly
10 that would be a component. In terms of the numbers, I
11 would sort of leave that up to the statisticians to
12 give me the best sort of estimate of what that should
13 involve. Clearly, I don't feel comfortable that I
14 know what the reproducibility of this test is on the
15 basis of two sites and 50 samples, most of which are
16 positive.

17 CHAIRMAN WILSON: Dr. Charache?

18 DR. CHARACHE: They should also include
19 some in which the MAI was a factor or that had a high
20 nil, to see how it came out when it was done in
21 different places. So I think it should be just a nice
22 gradient of tests, but I would also prefer the
23 statisticians selected it.

24 CHAIRMAN WILSON: Okay. Would you like to
25 comment?

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1 DR. CATANZARO: I would like to remind the
2 panel that while there was only that one formal study
3 comparing two laboratories, that the CDC trial was
4 conducted in five separate laboratories in five
5 different cities. The results of the five sites are
6 very uniform. So even though we didn't ship the
7 patients around from one place to another to get them
8 drawn in different labs, I think we can look to that
9 data and see that there are significant, there are
10 large numbers. If there was a significant variation
11 from one lab to another, I think it would have shown
12 up.

13 DR. NOLTE: You're talking about overall
14 performance?

15 DR. CATANZARO: I'm talking about overall
16 performance in five different laboratories as a
17 surrogate for how it might work in five different
18 laboratories. I mean it's a demonstration, I should
19 say.

20 The other comment I wanted to make about
21 reproducibility is that, while perhaps the exact study
22 that was suggested wasn't done, that the hard data on
23 the same individuals being tested over and over again
24 a half a dozen times with no variation over a period
25 of time -- it's not the same thing, but

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1 reproducibility is clearly very stable in that way.

2 CHAIRMAN WILSON: Any further comments?
3 Questions?

4 DR. NOLTE: One relatively -- I don't know
5 whether it is a small point or not. It is a point
6 that bothers me, but it has to do more with -- I am
7 looking for the slide.

8 DR. BARON: Could you speak into the
9 microphone, please?

10 DR. NOLTE: I'll try as soon as I find the
11 material.

12 DR. BARON: Okay.

13 DR. NOLTE: Basically, the decision
14 thresholds or the values that are used to determine
15 whether you have a valid test, there is this 1.5
16 international unit per milliliter for the mitogen
17 versus nil that's the minimum to have an acceptable
18 test? Am I stating that correctly?

19 Then we talked about being able to measure
20 a 15 percent human response with the limited detection
21 of the assay being 1.5 international units. I think I
22 posed this to the sponsor in a written form, and I
23 didn't understand your answer, so that's why I'm
24 asking again. It came up on Ms. Shively's slide as
25 well: that if that's the case, then don't you have to

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1 have a 10 international unit per ml minimum mitogen
2 versus nil response to be able to reliably measure a
3 15 percent --

4 DR. ROTHEL: Yes -- no, because you can
5 have a 1.5 international units per ml for the mitogen
6 and you can have a 1.5 IU per ml for the human PPD,
7 and get a 100 percent response and still be positive.

8 So it doesn't mean that you need to have 10 units in
9 your mitogen sample to get a positive answer, if that
10 is what you are inferring.

11 The mitogen is --

12 DR. NOLTE: That's what I'm worried about,
13 is having an acceptable test where you have 1.5
14 international units per ml and then 15 percent of that
15 being below your detectable limit, so missing a 15
16 percent response at the low end of your --

17 DR. ROTHEL: Sure, and that may be the
18 case, but the cutoff that's been used for all the
19 clinical trials, and were established very early on,
20 used that criteria, and that's what the data we have
21 presented has been done using that criteria. Sure, it
22 means that if your mitogen response is less than 10 IU
23 per ml, you need a response greater than 15 percent to
24 be positive in the test, but that same formula has
25 been used for all clinical trials.

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1 DR. NOLTE: How often do you find values
2 that are that cutoff for the 1.5 international units
3 per ml for the mitogen versus nil?

4 DR. ROTHEL: It would be less than 5
5 percent of the time, off the top of my head. We could
6 actually give you that figure accurately.

7 DR. NOLTE: Your colleague over there
8 is --

9 DR. ROTHEL: Do you know the figure, Tony?

10 DR. RADFORD: The answer is it's actually
11 a small number.

12 DR. ROTHEL: Talk into the microphone,
13 Tony.

14 DR. RADFORD: The answer is it's actually
15 a small number. I can tell you the CDC one group has
16 no risk, none. In the other risk groups, we can dig
17 it out, but I think in fact we're talking about two or
18 three. It's a very uncommon event.

19 DR. NOLTE: Thank you. I had the feeling
20 it was probably a small point, but I just wanted to
21 clarify.

22 The other thing that I find a problem in
23 terms of the interpretation of your test is the fact
24 that for an avium difference to be significant, it has
25 to be less than minus 10 percent. I actually gave

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1 that criteria to some of my colleagues in laboratory
2 medicine and then told them that, "Well, the
3 difference is minus 100 percent. Is that less than
4 minus 10 percent?"

5 DR. ROTHEL: Yes.

6 DR. NOLTE: And all of them got it wrong.

7 Now I realize that the absolute -- I mean it's a
8 difference of -- it's an algebraic problem, but I
9 think if you've got people interpreting this, a minus
10 100 percent difference is a significant difference.
11 At the face of it that is a larger number, not a
12 smaller number, to many people, including myself, and
13 I realize that's wrong mathematically, but
14 conceptually I think you might be better served by
15 having a different set of criteria for that part of
16 the test.

17 DR. ROTHEL: That's a very easy
18 mathematical calculation. We can change it to a
19 positive value if we want to. The truth of the thing
20 is that we will be preparing software to provide to
21 people who will be using this kit and having to get it
22 approved through the FDA, obviously.

23 DR. NOLTE: Yes, just don't convert it to
24 logs, okay?

25 (Laughter.)

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1 DR. ROTHEL: Yes. Done.

2 CHAIRMAN WILSON: Dr. Charache?

3 DR. CHARACHE: Yes, I'm just returning
4 again to the question of reproducibility of the test.
5 Again, from the CDC paper, there's only a single
6 variable that was associated with having a negative
7 skin test and a positive interferon assay, and that
8 single variable was if you were enrolled in site C.
9 On the other hand, there were three reasons for having
10 a positive skin and a negative interferon. One was
11 BCG vaccine; one was an avium complex assay, and the
12 third was enrollment in site E. So I do think we
13 really need to know about the relationships between
14 these different labs in terms of reproducibility of
15 testing.

16 It's not just enough when you add the
17 negative and the positive agreements together. We
18 really should know more about it.

19 CHAIRMAN WILSON: Thank you.

20 Yes, Dr. Lewinsohn?

21 DR. LEWINSOHN: Thank you.

22 I had a question that sort of related back
23 to what Dr. Catanzaro had said earlier in the sense of
24 this being, in a sense the clinical function being an
25 integrative one. It is true that we tend to look at

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1 the intensity of the TST test as being a surrogate for
2 true TB infection, certainly if it's greater than 15
3 millimeters or not, especially as we have been
4 debating whether to change the cutoff for those people
5 who we would consider to be low risk.

6 What I'm wondering is, is there a way to
7 report out the test that would give some more
8 information to clinicians? So, for example, you might
9 say it's positive, but like weak, strong, low, so that
10 a strong test might give you greater confidence in the
11 low-risk population that it's a true positive.

12 DR. CATANZARO: I think that's an
13 absolutely key factor, and, yes, the intention is to
14 report that it's positive and how positive it is.
15 Clinicians are always going to be faced with the
16 problem of having to integrate T-cell reactivity with
17 the rest of the analysis.

18 We have been talking about those cutoffs
19 of 5, 10, and 15 as if they're written in stone. In
20 fact, those 5, 10, and 15 have changed over my career
21 in medicine a great deal from time to time, and today
22 they're different from place to place. Those are the
23 criteria that we have been using that CDC has been
24 recommending.

25 I live in the State of California, which

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1 has a lot of the TB problem. The State of California
2 says we don't accept those criteria of CDC; we have
3 our own criteria for what we're going to interpret as
4 a positive or negative skin test. I don't want to
5 enunciate what those are. I simply want to say that
6 clinicians and public health officials will change
7 those cutoffs.

8 So this panel is not going to put those
9 cutoffs in stone now and forever, probably for a week
10 or two.

11 DR. LEWINSOHN: So the data that you would
12 get back would be like --

13 DR. CATANZARO: Quantitative.

14 DR. LEWINSOHN: -- the percentage human
15 response or something like that?

16 DR. CATANZARO: Yes.

17 CHAIRMAN WILSON: Dr. Cockerill?

18 DR. COCKERILL: This kind of goes back to
19 a question I probably wasn't clear about earlier this
20 morning. Is there any data that correlates the
21 positivity of the interferon gamma assay with the raw
22 measurement of the induration, the classification of
23 the scientist to the risk group and the
24 interpretation? Because that, to me, is probably a
25 better way of looking at this. We're mixing apples

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1 and oranges here because, as we just heard from Dr.
2 Catanzaro, over his career, and over mine too -- I'm
3 getting older -- the interpretation of the PPD has
4 changed. That's based on years and years of
5 experience.

6 So we're comparing two different assays
7 here, but the result for one of the assays is an
8 interpretation based on classification of risk group.

9 Am I on the right track here?

10 So is there any data that just basically
11 looks at induration? There was some in the handout, I
12 think, some correlative data looking at that
13 agreement, induration compared with the positivity of
14 the gamma interferon assay.

15 DR. ROTHEL: I think that our best
16 indication of that would be on the regression
17 comparing induration versus percentage of human
18 response. That's been done in the vast majority of
19 papers that have been published, and just about all of
20 them have found that there is significant association
21 with that regression. A couple of them have found no
22 great association, but in the vast majority, yes,
23 there is. The higher the induration, the higher the
24 same human response you will get.

25 CHAIRMAN WILSON: Okay, any other comments

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1 on the second question?

2 (No response.)

3 If not, could we have the third question?

4 The question states: "In which
5 populations of individuals could a positive or
6 negative QuantiFERON-TB assay provide clinical utility
7 alone or in conjunction with TST? Are there labeling
8 restrictions? If any, if it would add to clinical
9 utility for any population groups?"

10 Dr. Baron?

11 DR. BARON: Well, Dr. Nolte has already
12 talked about the fact that HIV-infected patients would
13 be another indication for labeling. So we think once
14 that group gets properly assessed, they should be
15 included in here and children as well.

16 CHAIRMAN WILSON: Other comments or
17 questions?

18 DR. NOLTE: I think we have touched on
19 this, but I mean the relationship between CD-4
20 positive cell counts in this assay is known? We
21 haven't seen the data, but I get the impression that
22 that data is available? Is that one way to deal with
23 this problem of using the assay in populations that
24 you have some concerns about in terms of being
25 immunocompromised? I mean the specific

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1 immunocompromised that we're worried about is
2 depressed CD-4 positive cell counts?

3 DR. ROTHEL: I suppose my answer is the
4 same as the answer I gave before. We do have a
5 considerable amount of data showing that it works
6 generally in cases of low CD-4 counts and HIV and
7 other compromised people, but we don't have sufficient
8 data to support its registration and approval by the
9 FDA. So we have to go and get more data. Probably
10 what we will do is a smaller study. We have a lot of
11 data already, but we need to do a working study in the
12 U.S. to extend that claim in the HIV-positive and
13 immunocompromised people.

14 I should add that --

15 DR. NOLTE: Is it a realistic way to think
16 about getting around this exclusion of
17 immunocompromised patients is to hang it sort of on
18 the CD-4?

19 DR. ROTHEL: Yes, I think that's quite an
20 appropriate way to do it. If a person's HIV-infected,
21 it doesn't mean they're immunocompromised.

22 DR. NOLTE: Right.

23 DR. ROTHEL: You should be looking at
24 their CD-4 count and relating performance to CD-4
25 count or some other measure of immuno-activity.

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1 DR. LEWINSOHN: Can I ask another
2 question?

3 CHAIRMAN WILSON: Dr. Lewinsohn.

4 DR. LEWINSOHN: So I guess this gets back
5 to that, I know admittedly, small number of patients
6 who got TST's and QuantiFERON tests, which seemed to
7 show more variability than you guys had seen when you
8 just did the repeated testing on an individual over
9 time, which in my mind raises this issue of whether
10 the TST and QuantiFERON tests could interfere with one
11 another or, specifically, whether the skin test
12 interferes with the QuantiFERON test.

13 So would you propose that that's a part of
14 the labeling, at least to make that suggestion, I mean
15 to suggest to do the QuantiFERON first then?

16 DR. ROTHEL: Yes, I agree. I think I
17 acknowledged that to you this morning, that we
18 probably should have made the labeling to say that you
19 shouldn't skin test within "X" number of days,
20 probably 30 days, the same as just for a skin test.

21 CHAIRMAN WILSON: Dr. Reller?

22 DR. RELLER: Although it's plausible that
23 patients with intact, or reasonably intact, CD-4
24 counts either before or after therapy would respond
25 like most other individuals, I would think until the

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1 data are in hand that one couldn't count on that.

2 Secondly, do you have any experience with
3 transplant populations? At least in this country a
4 growing number of patients, and a rich source of
5 clinical tuberculosis, sometimes recognized late, at
6 least are recognized in our center. So that,
7 theoretically, either before transplantation or at
8 some point you would want to know that. Do we know
9 what the effect of the whole range of
10 immunosuppressive agents to preserve transplanted
11 organs, what that does to this test?

12 DR. ROTHEL: No. That's a very good
13 question, and we haven't done it. That's why we've
14 contraindicated or limited the applications for those
15 individuals.

16 CHAIRMAN WILSON: Dr. Charache?

17 DR. CHARACHE: To address this
18 specifically, which is, in which populations of
19 individuals could a positive or negative assay through
20 clinical utility alone or in combination -- it seems
21 to me that if you have a negative test for either and
22 they have good, relatively good concordance in people
23 with active tuberculosis, it would be a suggestion
24 that you ought to look for other causes of the
25 patient's pulmonary disease and not assume that it's

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1 only tuberculosis.

2 I think there the caveat is that neither
3 is perfect. So you can't rule out TB. But it would
4 be highly suggestive, based on the data that we have,
5 that there is tuberculosis there.

6 In terms of looking for latent TB, I think
7 right now we would probably want to see what happens
8 with the change in the end-points moving up on the
9 curve, to get rid of a lot of the false positives,
10 because, hopefully, it would be useful there. But I
11 think right now it could be problematic in causing
12 overtreatment of a very large population.

13 CHAIRMAN WILSON: Thank you.

14 Yes, Dr. Cockerill?

15 DR. COCKERILL: Barth brings up a good
16 point about the transplant patients where we're
17 febrile and we're trying to figure out how the
18 investigation is going to go. If you have a negative
19 tuberculin skin test, the patients may be anergic. So
20 we will check anergy.

21 Is there any data with the mitogen control
22 with this assay as to mitogen-negative patients? Are
23 they anergic? Were any additional studies done?

24 The reason I am bringing that up is that,
25 if we have a mitogen-negative result, would it be

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1 possible to suggest that the patient have a full
2 complement of anergy skin testing? Is there any data
3 related to that?

4 DR. CATANZARO: I think before I let Jim
5 answer the question about the mitogen, I want to
6 remind you that CDC specifically recommends against
7 anergy testing to assist in the interpretation of
8 tuberculin skin tests. There's no correlation between
9 those two things, and they recently submitted an MMWR
10 advising people not to do that.

11 So I don't know if you want to comment
12 about that.

13 DR. COCKERILL: Thanks. I didn't know
14 that.

15 DR. ROTHEL: I can give you a little bit
16 of data on that study done in Kenya. We did, from
17 memory, I think 100 individuals, I think, and about 16
18 percent were HIV-positive and various CD-4 counts
19 ranging down to 6. We looked at the main mitogen
20 response of the individuals who were HIV-positive
21 compared to those that weren't and also stratified it
22 by CD-4. Yes, there definitely is a dropoff in
23 mitogen as a main response for all those individuals
24 with low CD-4 counts and with HIV infection.

25 But the trouble is there is variability.

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1 So a person can have a CD-4 count of 200 and have a
2 decent mitogen response, whereas a person with a CD-4
3 count of 1,500 can have a lower response than that.
4 So I don't think it's a definitive measure.
5 Definitely if a person hasn't got a mitogen response,
6 yes, you go looking.

7 CHAIRMAN WILSON: Other comments or
8 questions? Dr. Charache?

9 DR. CHARACHE: I'm just wondering, I was
10 just thinking about the mitogen as being a very nice
11 side offshoot of this test, knowing about it. Is the
12 mitogen stimulation quantification that's used here
13 adequate to predict anything about the ability of a
14 given patient to respond? Because you've got the data
15 anyway. Can you use it? Or do we know if you can use
16 it to predict responsiveness to mitogenic stimulation?
17 And is that data known for those that were PPD-
18 positive and interferon-test-negative?

19 DR. ROTHEL: I think Tony can address that
20 question specifically. I will just state that there
21 is something else we see as an application for the
22 QuantiFERON technology, is a totally different test
23 apart from TB, which we're here to talk about today,
24 which is a measure of immune-competence, but we would
25 use antigens other than mitogen.

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1 But Tony can address your question
2 specifically.

3 DR. RADFORD: Of course, as the ratio is
4 what's used, it's not dependent upon the actual
5 absolute mitogen response. We have, in fact, analyzed
6 the mitogen response and the TST positivity.

7 One of the interesting facts is that
8 you're twice as likely to be skin test positive if
9 your mitogen response is above 50 international units
10 per ml. However, we still don't believe we actually
11 have enough data on the HIV population to address
12 that.

13 CHAIRMAN WILSON: Any additional comments?

14 (No response.)

15 Okay, let's move to the fourth question.

16 The question states, "When the
17 QuantiFERON-TB assay is positive or negative and not
18 used in conjunction with TST, can available types of
19 data from the two clinical studies be used to
20 interpret the probability of TB infection for
21 individuals with low, moderate, or high risk?"

22 Dr. Baron?

23 DR. BARON: Can I clarify that question?
24 Do you mean all by itself without any other clinical
25 data?

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1 CHAIRMAN WILSON: Steve, do you want to
2 clarify the question?

3 MR. GUTMAN: Sure. The question, the
4 heart of the question, is: If this product is
5 approved, how to label it, what kind of message to
6 give to people who use it. So, yes, we are looking
7 for advice on how to characterize performance on the
8 labels, and we need to know what advice to give people
9 who might actually buy the test and use it.

10 DR. BARON: What does the skin test
11 labeling say? I mean, I can't believe it would say:
12 Here's your answer, all by itself. I am sure there
13 must be all kinds of caveats with it that say, "in
14 conjunction with a history" and "physical findings,"
15 and all those other things.

16 DR. ROTHEL: If I can briefly say, yes, it
17 does. Their labeling claims are nearly identical to
18 ours, and the diagnostic -- the detection of infection
19 with MTB, but then they have a whole lot of caveats in
20 interpreting in conjunction with all the clinical
21 findings, history, et cetera.

22 MR. GUTMAN: I think we have somebody from
23 CBER here who might be able to elucidate labeling
24 because that's obviously from a different shop, but
25 we'd be happy to share that.

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1 CHAIRMAN WILSON: Could you come to the
2 microphone, please, and identify yourself, please?

3 MR. MORRIS: Yes, I'm Sheldon Morris. I'm
4 the Chief of the Mycobacteria Lab at CBER. Frankly, I
5 don't have these labels memorized, but it basically
6 says, as an aid in the diagnosis of MTB infections,
7 and then it gives some caveats.

8 MR. GUTMAN: So I guess the question on
9 the table is what you would like to see in this
10 product. Do you want to see less? Do you want to see
11 more?

12 DR. BARON: Yes, it looks good as they had
13 proposed it in their written proposal with those
14 caveats.

15 CHAIRMAN WILSON: Any additional comments?
16 Dr. Nolte?

17 DR. NOLTE: I guess you're asking about
18 the statistics, I mean how to describe the
19 performance?

20 MR. GUTMAN: Well, I'm asking -- one way
21 to do that is not to describe it. It's to provide
22 just the most general contour of association. Another
23 is to eloquently and extensively describe it. We have
24 experience in the Division with both.

25 DR. NOLTE: I mean, clearly, they have

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1 data that addresses the performance characteristics of
2 the test relative to TST and the three groups that you
3 outlined there.

4 MR. GUTMAN: And would you like to
5 perhaps --

6 DR. NOLTE: I think it would be reasonable
7 to include that in the package insert.

8 CHAIRMAN WILSON: Dr. Ng?

9 DR. NG: I think the most illuminating way
10 of looking at this data was Dr. Sack's presentation of
11 Venn diagrams, because I think the user really wants
12 to know what the non-concordance rate is, if you're
13 just using a QuantiFERON assay and you don't have a
14 TST to compare it with.

15 CHAIRMAN WILSON: Dr. Cockerill?

16 DR. COCKERILL: But I presume that would
17 be modified based on the 30 percent, which we haven't
18 seen that data.

19 CHAIRMAN WILSON: Dr. Charache?

20 DR. CHARACHE: I think it should go
21 further than the current physicians' instruction
22 section, which has a paragraph on page 139, "The
23 possibility should not be excluded that a positive
24 QuantiFERON-TB test is due to a prior BCG
25 vaccination." It should also say that false positives

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1 exist or something, that it's not only BCG.

2 CHAIRMAN WILSON: Dr. Carroll?

3 DR. CARROLL: I would just like to
4 reiterate what Dr. Cockerill said. I would like to
5 see the Venn diagrams with the 30 percent cutoff,
6 particularly in that low-risk group. I think that
7 would be very helpful in terms of our comfort level
8 with that low-risk group and the false positivity
9 rate.

10 CHAIRMAN WILSON: Okay. Dr. Lewinsohn?

11 DR. LEWINSOHN: I was trying to think, I
12 mean, the sort of setting, I guess, that it seems like
13 we would most want to have this test would be in the
14 setting of something like a contact investigation
15 where we're really trying to tease out who's been
16 recently infected or not. Obviously, we can't really
17 tell who's truly infected, you know, where there is a
18 discordance between those two data.

19 So are there settings where it should be
20 recommended that you would do both tests, the hope
21 being that either would be sufficient or would you
22 propose that we would just do one or the other in that
23 kind of a setting? It's a question to you, sure.

24 DR. ROTHEL: I think the talk we heard
25 from Jim McAuley would say that it was perhaps a waste

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1 of time. In a real setting why would you use a skin
2 test and miss half of your results?

3 DR. LEWINSOHN: Well, but he's looking at
4 a different -- I mean he's screening for active
5 disease where there is high risk of spread. In a
6 contact investigation you're going to use your skin
7 test information to figure out kind of how far to go,
8 because each person who you find who's positive may
9 have been a contact. So that turns out to be very
10 practical there.

11 I'm just curious to know, would you do
12 both, the idea being that either one would be
13 sufficient to make you think they're a converter or --

14 DR. ROTHEL: My personal view would be,
15 no, I wouldn't, but I'll let Tony respond too.

16 DR. CATANZARO: I think it would be
17 tremendously burdensome to suggest to do both, and it
18 would be analogous to say, well, why not do all three?

19 Why not require Connaught, Tubersol, and QuantiFERON?

20 I think that would be a very burdensome thing to do.

21 I think that very nice data has been
22 presented here to show that the QuantiFERON is at
23 least as good as the tuberculin skin test, and the
24 physicians, the public health people can make a
25 decision based on their circumstances which one to do.

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1 Then regardless of which one they do, it's an aid to
2 the diagnosis; it has to be put in the clinical
3 context. Lots of other information has to be
4 collected before you go ahead and prescribe treatment.

5 So I think there's lots of safety leaving
6 it as it is, as an aid, and I would be horrified if
7 this panel recommended to do two or three tests every
8 time we wanted to ask the question: Does the patient
9 have latent tuberculosis infection?

10 CHAIRMAN WILSON: Dr. Cockerill?

11 DR. COCKERILL: If it's a false positivity
12 specificity issue in your low-risk group and your
13 incidence of a positive result for the QuantiFERON is
14 very low, then confirming that with a second test may
15 be reasonable. I'm not suggesting that, but based on
16 the data for the 15 percent cutoff, we see 7 versus 1,
17 I think, positive. There's a 12 percent agreement.
18 But the total number for that low-risk group is very,
19 very low, I think, in what I'm seeing.

20 So one could consider a two-tiered
21 approach, not suggesting that, especially if the 30
22 percent doesn't decrease that "false positivity."

23 CHAIRMAN WILSON: Dr. Reller?

24 DR. RELLER: I can see two tests when one
25 is very sensitive but lacks specificity, and there are

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1 ample models for this. But in this case I've seen no
2 data that suggests that they're really complementary,
3 and it would be to me defeating the whole purpose to
4 have two tests.

5 Each has its limitations, but unless there
6 were convincing data that you did one test and then
7 the other one added something to what you already had,
8 and vice versa, I think that would be the wrong way to
9 go, particularly one of the rationales for considering
10 this approach is all of the pitfalls with skin testing
11 in the first place in terms of followup, and quite
12 apart from interpreting, all of the things that have
13 already been discussed. So I think, from what I have
14 heard, the skin test and this test are not of the
15 genre that would be logically done in sequence.

16 CHAIRMAN WILSON: Dr. Charache?

17 DR. CHARACHE: I'd like to agree with both
18 Dr. Reller and Dr. Cockerill.

19 (Laughter.)

20 I'm going to suggest that in the high-risk
21 group they're close enough. So perhaps in the high-
22 risk group, since the sensitivity is better with the
23 skin test, if I got a negative with the interferon
24 assay, it might be worth doing the skin test, but not
25 on general populations, and that's going to be a small

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1 number of people.

2 I would say the reverse is true with the
3 lower-risk groups one and two of CDC and groups one,
4 two, and three of the WRAIR study. For those, if you
5 got a positive QuantiFERON test, it would be worth
6 confirming that it was really positive with a skin
7 test, because the skin test is going overcall
8 positives in the low-risk group, and it's, therefore,
9 a safety valve to get rid of the false positives.
10 Otherwise, we are going to have, with this only 12
11 percent agreement in the low-risk group, if you're
12 doing case studies, surveillance kinds of things, I
13 think it would be helpful to take that small
14 population which give you a positive QuantiFERON and
15 follow it with a skin test.

16 CHAIRMAN WILSON: Dr. Reller?

17 DR. RELLER: This is probably the only
18 time I've ever differed with Dr. Charache. To me,
19 there are three groups of patients: the one that
20 we're really worried about, and especially in a
21 patient population that I realize the test is not at
22 this point, would not, if approved, be approved for
23 use in HIV-positive transplant patients. But if I'm
24 really worried and the test is negative, I'm going to
25 pursue other things: bronchoscopy, whatever it is

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1 going to take clinically to get the diagnosis excluded
2 comfortably; that is, active disease excluded.

3 If it's a very low-risk population, I
4 think we're wasting time and effort on patients who
5 shouldn't be tested in the first place. And in the
6 middle group the test is as good or better than skin
7 testing or it shouldn't be approved for use, and if it
8 is, you realize that neither of them is going to be
9 perfect, and you do it. If things change in the
10 patient, you escalate the diagnostic process. But
11 you've got an opportunity, in passing through some of
12 the testing operations that we saw portrayed here, and
13 you do it and act appropriately on the results and get
14 on with things.

15 CHAIRMAN WILSON: Dr. Charache?

16 DR. CHARACHE: I'm sure this is the only
17 time I've disagreed with Dr. Reller.

18 (Laughter.)

19 Whenever we both have our hands up and
20 he's called first, I don't have to speak.

21 (Laughter.)

22 But I think in this case I'm very
23 concerned about the five- to tenfold increase in use
24 of prophylaxis for the latent TB possibility. Now I
25 don't know what that percentage will be when we look

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1 at different breakpoints. That may solve the problem.

2 But where we have such a low agreement,
3 unless the agreement is 80 percent or more, I think it
4 would be worth, rather than using prophylaxis, to do a
5 skin test, and certainly a lot less cumbersome to the
6 patient than the time they would need to be on
7 therapy.

8 CHAIRMAN WILSON: Dr. Cockerill?

9 DR. COCKERILL: Well, I agree with both.
10 I'm trying to maintain my friendship with both.

11 (Laughter.)

12 But I would agree that, first of all, most
13 of us would not be doing risk one testing except for
14 contacts. So if we do it in that context, that this is a
15 contact that we're screening, putting aside the Army
16 and whoever else is screening probably inappropriately
17 for the risk one, you will have six more with a cutoff
18 of 15 versus 1 in this group, and I don't know what
19 that percentage is, that will then, based on current
20 recommendations -- and I'm not up-to-date on all the
21 CDC recommendations -- you would treat with either six
22 months of Isoniazid or two months of the combined.

23 That, to me, if we would stay at a 15
24 percent, one would then consider another test to
25 substantiate that result. I don't know what that

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1 total incidence is, but it probably is pretty low.
2 Even though we have that discordance and the agreement
3 is only 12, there were very few that actually tested
4 positive, either one, in that risk group one.

5 Now the 30 percent cutoff, when we see
6 that data, maybe we'll get down to 3 versus 1, and
7 then I agree with what you're saying.

8 CHAIRMAN WILSON: Dr. Sanders?

9 DR. SANDERS: Two comments -- actually,
10 two questions. Although I agree with Dr. Charache's
11 recommendations for potentially handling the risk
12 groups, are we saying that this is a recommendation
13 we're actually making and asking that to be printed in
14 the package insert, if ultimately approved, or are we
15 making this as a recommendation that could be
16 considered by physicians treating the patient who
17 actually has that patient in front of them to
18 consider? So that's one question.

19 And then the other has to do with, we
20 continue to speak about the 15 percent and the 30
21 percent cutoff, which we have not seen the 30 percent
22 data. So I guess the other question is: Are we going
23 to make a recommendation today, having not seen that
24 data?

25 CHAIRMAN WILSON: Do you want to comment,

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1 Dr. Charache?

2 DR. CHARACHE: Yes. I think before we
3 make any recommendation of follow-up testing, the most
4 important points to be made are those that you and Dr.
5 Reller have made, which is the individual physician
6 will be assessing the patient. But I think guidance
7 should be given.

8 Now in terms of making a recommendation of
9 switching the cutoff to this 30 percent rather than
10 15, I would recommend that the recommendation be made
11 that the cutoff be reviewed for each category of
12 patient and be adjusted to optimize the purpose for
13 which the test is to be performed. So if the purpose
14 of the low-risk group is to determine who would
15 benefit from antibiotic therapy, then the breakpoint
16 should be set to optimize getting that information.
17 But I don't think we're in a position to recommend
18 what the numbers should be.

19 CHAIRMAN WILSON: Would you like to make a
20 comment?

21 DR. JOLLY: Thank you, Mr. Chairman.

22 I would draw the panel's attention to the
23 document which starts on page 192 of volume 2. In
24 that particular analysis we do present all of the data
25 for 15 percent cutoff and for 30 percent cutoff. I

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1 refer in particular to page 196, where there's a table
2 which shows precisely the Venn diagrams of the FDA,
3 not Venn diagrams but these tables, at the 15 percent
4 cutoff and at the 30 percent cutoff.

5 I would like to draw the panel's attention
6 to the fact that the specificity in each of those
7 three risk groups changes to 98 percent, 98 percent,
8 and 94 percent, respectively, when we move the cutoff
9 from 15 to 30 percent. This is precisely the reason
10 that we recommended the change to 30 percent, because
11 we believe it matches these data precisely.

12 In terms of maximizing, why was that 30
13 percent chosen? I draw the committee's attention to
14 the rest of that document which says that the 30
15 percent cutoff is appropriate for -- was chosen as
16 being the appropriate cutoff point based on the CDC
17 data.

18 So I would submit, Mr. Chairman, that
19 those are right there and we would draw the panel's
20 attention to those data.

21 CHAIRMAN WILSON: Thank you.

22 Dr. Charache?

23 DR. CHARACHE: Just in reading that, the
24 table is set up and I want to be sure that I'm reading
25 it correctly. What this is saying is that, of those

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1 that are skin-test-positive -- there are four that
2 were skin-test-positive -- there were 41 that were
3 positive by the QuantiFERON?

4 DR. JOLLY: That's correct, but that's
5 with a cutoff of 10 percent.

6 DR. CHARACHE: Then as we go across, the
7 differences are a threefold change?

8 DR. ROTHEL: If you go --

9 DR. CHARACHE: Of discrepant results.

10 DR. JOLLY: -- to 30 percent, then it's
11 six are in the discordant group --

12 DR. CHARACHE: Right.

13 DR. JOLLY: -- as opposed to two.

14 DR. CHARACHE: This is the Army recruits
15 or the Navy recruits?

16 DR. JOLLY: This is correct.

17 DR. CHARACHE: So we would also like to
18 see this in the other broader population, but this is
19 exactly the kind of data that I'm sure the FDA and the
20 sponsor will be looking at in terms of selecting the
21 right cutoff.

22 This is just the low group, and then
23 intermediate group we would be concerned about as
24 well, where there's quite a few discrepant as well.

25 DR. JOLLY: Thank you.

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1 MR. GUTMAN: Our statistician would like
2 to make a comment.

3 CHAIRMAN WILSON: Okay.

4 MR. DAWSON: I have to take exception to
5 the company's analysis arriving at the 30 percent
6 cutoff for human response. It's based on ROC
7 analysis, and, of course, that's a wonderful tool for
8 deciding on a cutoff because you get to look at the
9 whole spectrum of possible cutoffs and pick the one
10 that gives you a desirable balance between sensitivity
11 and specificity.

12 But the problem with what the company has
13 done is to base their ROC entirely on a comparison
14 with TST as a gold standard. All I can say is we
15 can't interpret the result because we all in this room
16 know or believe, or have certainly heard today, that
17 TST is not a gold standard. So I basically would ask
18 you to disregard anything related to those ROC figures
19 in your panel pack.

20 As I mentioned this morning, we do have
21 analytical means available to us for evaluating an
22 after-the-fact change in the cutoff. It's a cross-
23 validation method involving a technique known as the
24 bootstrap. So if the company, for whatever reason,
25 wants to change the cutoff, in this case from 15 to 30

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1 percent, we can recommend an appropriate technique,
2 but that technique would be what I would expect would
3 have to be done for justification.

4 CHAIRMAN WILSON: Thank you.

5 Any other questions or comments?

6 (No response.)

7 Question No. 5, please.

8 Question No. 5 states: "Could conjunctive
9 or adjunctive use of QFT with TST testing provide
10 additional benefit in any of the above risk groups?"

11 I think we've discussed this to some extent, but are
12 there any additional comments or questions?

13 Dr. Lewinsohn?

14 DR. LEWINSOHN: I guess if we're still
15 kind of talking about labeling, I mean it seems like
16 having the data certainly is, from both of the
17 American studies along with the Venn diagrams, would
18 be very helpful for the clinician. It seems to me,
19 though, that we don't ultimately really know many of
20 the answers that we would like to know in terms of
21 who's likely to go on to develop active disease after
22 they have either one of these tests turn up positive.

23 I suspect those answers will come out with more study
24 and more clinical evaluation. So that it might be
25 smart just to have data, but a paucity perhaps of

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1 specific clinical recommendations in the package
2 insert.

3 CHAIRMAN WILSON: Dr. Carroll?

4 DR. CARROLL: Yes, I just wanted to say
5 something similar. As a clinician, I do not think
6 that the labeling should include a recommendation for
7 TST testing in conjunction with this assay. I think
8 that should be left up to the individual physician's
9 decision and the risk stratification of the patient
10 and other data that will be used to decide whether a
11 patient has active disease or is at low risk for
12 disease.

13 So I would disagree with actually
14 including that in the labeling. I would say, though,
15 that all information should be provided to the
16 clinician or the labeling regarding discordance for
17 each of the risk groups.

18 CHAIRMAN WILSON: Mr. Reynolds?

19 MR. REYNOLDS: I again have a question on
20 the current labeling for the PPD. What does that say
21 about testing in low-risk groups? Anyone have any
22 idea?

23 CHAIRMAN WILSON: Does anyone from FDA
24 want to comment on that?

25 DR. CATANZARO: I don't know the labeling,

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1 but I know CDC's recommendations quite well. They
2 recommend specifically against that. CDC recommends
3 targeted testing, as does the IOM, targeting based on
4 epidemiologic factors. As someone pointed out, that
5 doesn't forbid anybody from using them in a low risk,
6 and that causes problems in interpretation that a
7 clinician has to spend a lot of time on, but CDC
8 recommends targeted testing.

9 MR. GUTMAN: I do have, compliments of a
10 panel member, the package insert, and the CBER person
11 will quality control me, but it looks relatively
12 nondirective.

13 CHAIRMAN WILSON: Thank you.

14 DR. COCKERILL: It does recommend
15 additional testing, culture, chest x-ray based on
16 clinical findings.

17 CHAIRMAN WILSON: Dr. Charache?

18 DR. CHARACHE: I think it would be helpful
19 to provide guidance which is accurate with any changes
20 that are being made in breakpoints, because I don't
21 know that the average physician would understand how
22 to use the data. We're struggling with how to
23 interpret it here, and when you emphasize the
24 agreement on the positives and when you emphasize the
25 agreement on the negatives. I think that that's a lot

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1 to ask of someone who's, whether he's doing the case
2 study or taking care of a family member of someone
3 who's had TB, or whatever it is. So I think some
4 guidance would be helpful.

5 But I think, as Dr. Sanders pointed out,
6 this should also be emphasized in terms of the overall
7 responsibility of the physician in deciding what's
8 best for that patient.

9 CHAIRMAN WILSON: Any other comments? Dr.
10 Cockerill?

11 DR. COCKERILL: Yes, I would agree with
12 that because, as a clinician as well, we do have
13 guidelines for interpreting the tuberculin skin test
14 which aren't part of the package insert. We don't
15 have guidelines for interpreting this test outside of
16 the package insert. So anything that we can provide,
17 especially if we have two different cutoffs, that
18 information has to be in there as far as, what is a
19 low risk, moderate, high risk, for the clinician to
20 make some sense out of it.

21 CHAIRMAN WILSON: Okay, again, in an
22 effort to help everyone get to the airport on time
23 today, I'm going to rearrange the agenda somewhat. I
24 would like at this point to go to the open public
25 hearing. If any members of the audience would like to

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1 make a comment, please come forward at this time.

2 (No response.)

3 There being none, the open public hearing
4 is closed.

5 I spoke briefly with industry over the
6 lunch hour. They were hoping to have a little bit of
7 time to prepare the industry response. So what I
8 would like to do now is take a break from now until
9 2:30 to allow them at least 15 minutes to work on
10 that, if you would like to take that time.

11 DR. ROTHEL: I think we would just like to
12 thank the panel for their considerations today, and
13 we're quite happy. Thank you.

14 CHAIRMAN WILSON: Okay. Does FDA need
15 time to do anything to prepare their response?

16 MR. GUTMAN: No, we have no response.

17 CHAIRMAN WILSON: You have no response?
18 Okay.

19 At this time let's move forward, then,
20 with the final recommendations and vote. At this time
21 it's the responsibility of the panel to provide final
22 recommendations to the FDA and to vote on the product
23 that is before us today. I would like to remind
24 everyone that only voting and temporary voting members
25 can vote.

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1 Before we get there, I just want to make
2 sure that if there are any last issues that the panel
3 members have that they would like to clarify prior to
4 the final recommendations and vote, we could do that
5 now.

6 Dr. Nolte?

7 DR. NOLTE: Yes, we were talking about
8 having guidelines or recommendations for how to
9 interpret tests that were outside of the package
10 insert. Clearly, there are guidelines for
11 interpreting tuberculin skin testing that has come
12 from the CDC and other places.

13 I wonder, since the CDC was so intimately
14 involved with the clinical trial of this particular
15 test, whether there are going to be guidelines
16 forthcoming soon from them in terms of how to
17 interpret such a test, should it be approved.

18 DR. MAZUREK: Jerry Mazurek, CDC.

19 Yes, we're working on it.

20 DR. NOLTE: Okay.

21 CHAIRMAN WILSON: Does anyone on the panel
22 feel like they need any time to look at any more of
23 the data, particularly the article that was passed out
24 today?

25 Dr. Ng?

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1 DR. NG: Dr. Mazurek, I would be very
2 interested in seeing the interlaboratory
3 reproducibility before the CDC comes out with its
4 guidelines. In other words, I want to know how
5 reproducible a 15 or a 30 percent cutoff is from lab
6 to lab.

7 DR. MAZUREK: For additional studies and
8 studies that are coming up for the QuantiFERON, we
9 will try to take that into account and include
10 reproducibility and interlaboratory variations in
11 assessing the test.

12 CHAIRMAN WILSON: Okay. Ms. Poole?

13 MS. POOLE: Good afternoon. I'll now read
14 the panel recommendations, all voted options.

15 "The medical devices amendments to the
16 Federal Food, Drug and Cosmetic Act (the Act) as
17 amended by the Safe Medical Devices Act of 1990 allows
18 the Food and Drug Administration to obtain a
19 recommendation from an expert advisory panel on
20 designated medical devices pre-market approval
21 applications that are filed with the agency.

22 "The PMA must stand on its own merits, and
23 your recommendations must be supported by safety and
24 effectiveness data in the application or by applicable
25 publicly-available information. Safety is defined in

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1 the Act as a reasonable assurance, based on valid
2 scientific evidence, that the probable benefits to
3 health under conditions of intended use outweigh any
4 probable risk. Effectiveness is defined as a
5 reasonable assurance that in a significant portion of
6 the population the use of the device for its intended
7 uses and conditions of use, when labeled, will provide
8 clinically-significant results.

9 "Your recommendation options for the vote
10 are as follows: approval, if there are no attached
11 conditions; approvable with conditions. The panel may
12 recommend that the PMA be found approvable subject to
13 specified conditions such as physician or patient
14 education, labeling changes, or a further analysis of
15 existing data. Prior to voting, all of these
16 conditions should be discussed by the panel.

17 "A vote of not approvable, the panel may
18 recommend that the PMA is not approvable if the data
19 do not provide a reasonable assurance that the device
20 is safe or if a reasonable assurance has not been
21 given that the device is effective under the
22 conditions of use prescribed, recommended, or
23 suggested in the proposed labeling.

24 "Following the vote, the Chair will ask
25 each panel member to present a brief statement

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1 outlining the reasons for their vote."

2 Our voting members are Kathleen Beavis, Valerie
3 Ng, Natalie Sanders, and appointed as temporary voting
4 members -- and we have another citation to read:

5 "Pursuant to the authority granted under the
6 Medical Devices Advisory Committee charter dated
7 October 27th, 1990, and as amende August 18th, 1999, I
8 appoint the following persons as voting members of the
9 Subcommittee of the Microbiology Advisors Panel for
10 the duration of this panel meeting on October 12th,
11 2001: Ellen J. Baron, Frederick Nolte, and Barth
12 Reller.

13 "For the record, these people are special
14 government employees and are either a consultant to
15 this panel or a voting member of another panel under
16 the Medical Devices Advisory Committee. They have
17 undergone the customary conflict-of-interest review.
18 They have reviewed the material to be considered at
19 this meeting."

20 And it is signed "David W. Feigal, M.D.,
21 MPH, Director for the Center for Devices and
22 Radiological Health," on October 10th of this year.

23 CHAIRMAN WILSON: Thank you.

24 Are there any questions from members of
25 the panel?

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1 (No response.)

2 All right, then at this point I will
3 entertain motions regarding this PMA submission. Dr.
4 Baron?

5 DR. BARON: I move that we vote for
6 approvable with conditions, and I hope the panel will
7 help me with the conditions here.

8 DR. SANDERS: I'll second that.

9 CHAIRMAN WILSON: Okay, we need to specify
10 the conditions then.

11 DR. BARON: Karen has handed me a few.

12 Attached conditions should be statistical
13 analysis, as suggested by Dr. Dawson and originally by
14 Dr. Charache, about stratification of risk groups and
15 appropriate cutoffs; interlaboratory reproducibility
16 studies previewed and then followed by CDC guidelines
17 for use external to the package insert, independent of
18 the package insert.

19 CHAIRMAN WILSON: Dr. Gutman, I don't
20 believe we can specify --

21 MR. GUTMAN: You can recommend that, but
22 don't make that a condition of approval.

23 DR. BARON: Okay, and one more before I
24 stop: physician recommendations for utilization of
25 the results.

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1 DR. SANDERS: Actually, I would like to
2 modify that last one and ask for a physician education
3 program to educate physicians, treating physicians,
4 about the test. I know that there's probably a
5 program in place for the laboratory physicians in
6 order to be able to ultimately report and interpret
7 the results, but an additional physician or practicing
8 physician education program.

9 DR. NOLTE: In addition to any CDC
10 recommendations that might be forthcoming?

11 DR. SANDERS: Well, we can't mandate that
12 part, but we can ask the company to provide physician
13 education.

14 DR. NOLTE: No, I'm asking you in terms,
15 if there were CDC guidelines forthcoming, would you
16 have the same recommendation?

17 DR. SANDERS: If there were CDC guidelines
18 forthcoming, I would accept those.

19 CHAIRMAN WILSON: Okay, we have a motion
20 of approvable with conditions, those conditions being
21 that there be further statistical analysis with
22 stratification of the risk groups by the varying
23 cutoffs; that there be further data provided on the
24 reproducibility, particularly regarding
25 interlaboratory variability in test results, and the

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1 third one being recommendations for physician
2 interpretation and education regarding the use of the
3 product.

4 Dr. Ng?

5 DR. NG: I would ask that there be
6 expansion in your package insert for people like me,
7 so when I use it, I have the different risk groups and
8 the concordance and non-concordance of the two tests,
9 so I can explain to my users.

10 CHAIRMAN WILSON: Dr. Baron?

11 DR. BARON: Dr. Charache is suggesting
12 that we also add that data be presented in the package
13 insert on the agreement of positives.

14 DR. CHARACHE: I shouldn't be speaking.
15 May I speak? No, I shouldn't speak?

16 CHAIRMAN WILSON: No, you can't speak.

17 DR. BARON: Okay, she's suggesting that we
18 add agreement not just on the positives and negatives,
19 but data presented separately.

20 DR. SANDERS: Mr. Chairman, is it not our
21 usual practice, after we have made our final
22 recommendation and vote, that we then go through the
23 package insert in greater detail? Is that our usual
24 practice or do we do it now?

25 CHAIRMAN WILSON: We do it now.

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1 DR. SANDERS: Well, if we do it now, I
2 think also we had discussed earlier that we would be
3 careful about the timing, if skin testing had been
4 performed, that there should be perhaps a warning or a
5 limitation indicated in the package insert of a
6 timeframe with which not to perform the QFT. So that
7 should also be added in the package insert.

8 CHAIRMAN WILSON: Dr. Baron, could you
9 further clarify what additional data that you were
10 suggesting be included?

11 DR. BARON: Well, it's not my suggestion.

12 (Laughter.)

13 CHAIRMAN WILSON: Yes, but you made the
14 motion.

15 DR. BARON: I made the motion, but I don't
16 quite understand it.

17 (Laughter.)

18 CHAIRMAN WILSON: We need to know before
19 we can make a recommendation to the manufacturer --

20 DR. BARON: Can some other committee
21 member agree with it or not, and then --

22 CHAIRMAN WILSON: Dr. Ng?

23 DR. NG: If I can interpret what I think
24 Dr. Charache was asking, it's the two-by-two tables,
25 because the agreement is looking at that diagonal axis

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1 of what in boxes A and D in the two-by-two table.
2 What I was asking for was slightly different, which
3 was the overlap and the missed populations between the
4 two tests. But if we include all that information, it
5 would really help with the interpretation of the test
6 result.

7 DR. RELLE: So what Dr. Ng is talking
8 about is basically the two-by-two tables plus the Venn
9 diagrams?

10 CHAIRMAN WILSON: Correct. Okay, so we
11 have a motion, then, for approval with conditions, and
12 so far there are, depending on how you slice it, five
13 or six conditions.

14 Dr. Reller?

15 DR. RELLE: I'm assuming that in those
16 conditions are the explicit description of the
17 populations for which data are not yet available:
18 transplant, et cetera. I think this is very important
19 because with a new test that is more -- the scientific
20 basis of it is more delineated. You're recalling
21 memory from lymphocytes with a purified protein
22 derivative of what you are seeking to elicit the
23 memory of, that there is maybe an assumption that it's
24 a better test.

25 With the CDC guidelines and more

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1 experience, it may turn out to be that way, but I can
2 envision a situation where in the very patients for
3 which there are no current data would be the very
4 patients that Dr. Ng and others, including ourselves,
5 would be pounded upon to do the test. I think that it
6 should be very explicit, and then to come in
7 subsequently, as the data unfolds and the guidelines
8 are clarified, but to have that unequivocally spelled
9 out in the package insert, so that there would be a
10 sequenced introduction that was consonant with the
11 database available.

12 CHAIRMAN WILSON: Thank you. Is there any
13 further discussion of the conditions? Dr. Sanders?

14 DR. SANDERS: Well, I just want to make a
15 comment that that actually, those limitations are
16 actually spelled out as the company has given it to
17 us, and I would be very surprised if they were not
18 already planning to look at this in those populations.

19 CHAIRMAN WILSON: We have a motion and we
20 had a second on the original motion. At this point I
21 would need a motion on the amended conditions. Does
22 everyone have firmly set what all the conditions are
23 or would you like me to go over those again?

24 First is further statistical analysis,
25 particularly regarding stratification of the data by

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1 the different risk groups and the varying cutoff
2 points.

3 Second is the issue of reproducibility,
4 particularly regarding interlaboratory variability.

5 The third is information regarding
6 interpretation of the tests, both by laboratory
7 physician or scientists as well as the practicing
8 clinician.

9 The next is inclusion of further data,
10 both the Venn diagrams as well as the two-by-two
11 tables.

12 And the final one is that there be a
13 comment regarding the possible effect of tuberculin
14 skin testing on the QFT test and the need for possibly
15 separating those two.

16 DR. BARON: Can I clarify the
17 interlaboratory reproducibility studies, that they
18 should include a lot of negatives. It's the false
19 positives we're concerned about here.

20 DR. NOLTE: I think it needs to include a
21 whole range, the range of expected values and sort of
22 representative of what you might see in a population
23 that you were screening. I know this is different;
24 we're talking about different populations here, but
25 something more representative of what you might

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1 actually wind up testing.

2 CHAIRMAN WILSON: Okay, thank you.

3 DR. NOLTE: I need a clarification on this
4 physician education aspect of this and how this
5 becomes a condition to approval. I mean, what are we
6 suggesting when we say this, that the manufacturer
7 contact each and every practicing physician and tell
8 them how to interpret this or what? I mean, to do
9 education programs? What are we buying into here by
10 physician education?

11 MR. REYNOLDS: I was thinking something
12 more along the line of a little booklet or leaflet or
13 something that could be given out to physicians,
14 explaining in more detail how this test works and how
15 it should be interpreted. I don't know what the other
16 folks on the committee were thinking of.

17 DR. SANDERS: Since I made that
18 suggestion, actually, that's what I envision. But I
19 envision it in two ways: one, that as this test
20 becomes purchased by entities, there would be an
21 education process for the laboratory and the
22 supervising physician or lab director at that
23 institution.

24 I would also envision, subsequently, some
25 type of program for instructing the using clinicians,

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1 with materials provided by Cellestis. Now I'm not
2 saying that Cellestis has to actually come out and do
3 that education program, but with materials provided by
4 Cellestis. That could actually be done by the lab
5 director or the lab director's staff, because once
6 that test has been purchased by the entity, they're
7 going to want people to use it.

8 So that is how I had envisioned. Does
9 that help you, Dr. Nolte?

10 DR. NOLTE: Yes, I guess it does, but I'm
11 just trying to think if there really are going to be
12 guidelines, of course, coming from CDC, it's hard to
13 see how the information from the sponsor is going to
14 have --

15 DR. SANDERS: I made that recommendation
16 because I do feel that clinicians will need to be
17 educated on how to use this test.

18 DR. NOLTE: Yes.

19 DR. SANDERS: And we could not, for the
20 record, state that we would encourage CDC, another
21 government agency, to do this. So we would have to
22 then make it a recommendation for the sponsor.

23 DR. NOLTE: We've also asked them to
24 include a lot of that type of information in the
25 package insert. So I'm trying to figure out what this

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1 pamphlet from the sponsor is going to say that's not
2 in the package insert.

3 DR. SANDERS: Well, as a treating
4 physician, I actually never see the package insert for
5 a lab test that I order.

6 DR. NOLTE: No, I understand that. I
7 understand that, but whose responsibility is it to
8 educate, the sponsor or the offering laboratory?

9 CHAIRMAN WILSON: Dr. Gutman?

10 MR. GUTMAN: Yes, we're prepared to work
11 with the company and also to consult with CDC and try
12 and create some path for it. I think you are trying
13 to micromanage. You've made a recommendation. We'll
14 try and take it to heart.

15 DR. NOLTE: Okay.

16 CHAIRMAN WILSON: We have a motion for
17 approvable with conditions. I need a second on the
18 conditions as clarified.

19 DR. NG: Second.

20 CHAIRMAN WILSON: We have a motion and a
21 second. Is there any further discussion at this time
22 regarding either the main motion or the conditions?

23 (No response.)

24 Okay, there being none, then I would like
25 to take the vote. All the voting panel members who

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1 are in favor raise their hand.

2 (Show of hands.)

3 Do it by voice as well? Shall we do it
4 again?

5 Dr. Reller?

6 DR. RELLE: Reller, yes.

7 CHAIRMAN WILSON: Dr. Nolte?

8 DR. NOLTE: Nolte, yes.

9 CHAIRMAN WILSON: Dr. Beavis?

10 DR. BEAVIS: Beavis, yes.

11 DR. NG: Ng, yes.

12 DR. SANDERS: Sanders, yes.

13 DR. BARON: Oh, Baron, yes.

14 CHAIRMAN WILSON: The vote is unanimous.

15 Thank you.

16 Okay, at this point then we would like to
17 move to have each of the voting members state the
18 reason for their vote, beginning with Dr. Reller.

19 DR. RELLE: I believe the data presented
20 justified the recommendation and the vote that we have
21 just taken.

22 CHAIRMAN WILSON: Dr. Nolte?

23 DR. NOLTE: Yes, obviously, I think this
24 test represents an advance in terms of its intended
25 use, and the issues that I have in terms of the data

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1 were essentially around the statistics to validate the
2 30 percent cutoff and the interlaboratory
3 reproducibility, and both of those have been addressed
4 in the conditions we attached.

5 CHAIRMAN WILSON: Dr. Beavis?

6 DR. BEAVIS: I want to thank and commend
7 the sponsors for tackling, I think, a very difficult
8 area and a severe public health issue in this country,
9 especially being from Cook County.

10 Again, I think the data are very strong
11 and that the additional data will only further support
12 the use of this test.

13 CHAIRMAN WILSON: Dr. Ng?

14 DR. NG: I voted yes because anything has
15 to be better than the skin test.

16 (Laughter.)

17 CHAIRMAN WILSON: Dr. Sanders?

18 DR. SANDERS: I would agree with the
19 opinions that have already been expressed from my
20 colleagues. Thank you.

21 CHAIRMAN WILSON: And Dr. Baron?

22 DR. BARON: I want this test. Also, I
23 like the idea of having it be a laboratory test that I
24 can charge somebody for.

25 (Laughter.)

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1 CHAIRMAN WILSON: All right, thank you.

2 That concludes the business for today. I
3 would, in particular, like to thank the sponsor. I
4 think this was a very well-done submission, both in
5 terms of the written material as well as their
6 presentations today. I would really like to applaud
7 the efforts that they have made.

8 I would like to thank all the panel
9 members, particularly our guest, Dr. Lewinsohn, who
10 had to leave a few minutes ago, could not stay, had to
11 make a flight; all the members of the FDA for all the
12 work they've done on this. This has been a very good
13 meeting.

14 I would like to particularly thank
15 everyone who made the efforts to get here in these
16 trying times. Travel is not easy right now. I know
17 what it's like, and we do appreciate everybody who's
18 willing to fly at a time like this.

19 Thank you, and the meeting is adjourned.

20 (Whereupon, at 2:36 p.m., the meeting was
21 adjourned.)

22

23

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