

FOOD AND DRUG ADMINISTRATION

Science Board

Meeting

April 13, 2001

9:00 a.m.

U.S. FDA Building
CDER Conference Room
Room 1066
5630 Fishers Lane
Rockville, Maryland

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Members of the Science Board to the FDA

Robert S. Langer, ScD. (Chair)
Massachusetts Institute of Technology

Cecil Pickett, Ph.D.
Executive Vice President, Schering-Plough Institute

Rita Colwell, Ph.D., D.Sc. (Hon.)
Director, National Science Foundation

Marion Nestle, Ph.D., M.P.H.
New York University, Professor and Chair
Department of Nutrition and Food Studies

Owen Fennema, Ph.D. Professor Emeritus
Department of Food Science, University of Wisconsin

Martin Rosenberg, Ph.D.
Senior Vice President and Director
SmithKline Beecham Pharmaceutical
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Edward M. Scolnick, M.D., President
Merck Research Laboratories

Robert M. Nerem, Ph.D., Professor and Director,
Institute of Bioengineering and Bioscience
Georgia Institute of Technology

Harold Davis, D.V.M., Ph.D.
Amgen

Marion W. Anders, D.V.M., Ph.D.
Professor and Chair
Department of Pharmacology
University of Rochester

Michael P. Doyle, Ph.D.,
Professor and Department Head
Department of Food Science and Technology
Center for Food Safety and Quality Enhancement
University of Georgia

Presenters and Meeting Participants

Bernard A. Schwetz, Ph.D., Acting Deputy
Commissioner, FDA, and Senior Advisor for Science

Robert Buchanan, Senior Science Advisor and Director,
Office of Science, CFSAN

Dan Casciano, Ph.D., Acting Director of NCTR

David Feigal, Ph.D., Director of the Center for
Devices and Radiological Health

Dennis Baker, Ph.D., Associate Commissioner for
Regulatory Affairs

Margaret Miller, Ph.D., OWH

Suzanne Fitzpatrick, Ph.D., FDA

Linda A. Suydam, Senior Associate Commissioner, FDA

Alan M. Rulis, Ph.D., Director, Office of Premarket
Approval, CFSAN

Dennis Keefe, Ph.D., Assistant to the Director of
Premarket Approval, CFSAN

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P R O C E E D I N G S

1
2 DR. LANGER: I'd like to call the
3 meeting to order.

4 Today we've invited a guest from the
5 FDA's National Center for Toxicological
6 Research Science Advisory Board to share his
7 views and participate in the Board's
8 discussion.

9 Dr. Pickett is the Executive Vice
10 President for Discovery Research at the
11 Schering-Plough Research Institute.

12 So what I'd like to do to start us, he
13 could introduce himself, have the rest of the
14 Board members go around the table to introduce
15 themselves, and then continue around to the FDA
16 participants.

17 DR. PICKETT: Good morning. Dr. Cecil
18 Pickett from the Schering-Plough Research
19 Institute. I have responsibility for drug
20 discovery and some of the preclinical
21 development.

1 DR. NEREM: I'm Bob Nerem from Georgia
2 Tech, I'm Cecil's right hand man.

3 (Laughter)

4 DR. NESTLE: I'm Marion Nestle, I'm
5 Professor and Chair of the Department of
6 Nutrition and Food Studies at the New York
7 University.

8 DR. DAVIS: Harold Davis, Vice
9 President of Preclinical Safety Assessment at
10 Amgen, pharmacokinetics, toxicology,
11 regulatory.

12 DR. DOYLE: I'm Mike Doyle, I'm a
13 Professor and Director of the Center for Food
14 Safety at the University of Georgia.

15 DR. FENNEMA: Owen Fennema, Emeritus
16 Professor, University of Wisconsin, a fully-
17 occupied professional.

18 DR. ROSENBERG: Marty Rosenberg, of
19 the newly merged company of Glaxo Smithkline --
20 trying to figure out which side of the company
21 I work in.

1 DR. SCOLNICK: Ed Scolnick, head of
2 R&D at Merck.

3 DR. ANDERS: Greg Anders, Professor
4 Emeritus, and contrary to what -- at the
5 University of Rochester. Sort like Owen, I'm
6 running the myth of part-time employment.

7 DR. SCHWETZ: I'm Bernard Schwetz; I'm
8 not a Science Board member. We'll come back to
9 that in a couple minutes.

10 DR. LANGER: Bob Langer.

11 DR. JACOBSON: Liz Jacobson, I'm
12 Acting Senior Advisor for Science at FDA.

13 MS. BOND: Susan Bond, Executive
14 Secretary to the Board. And just a reminder to
15 make sure you speak into the microphones, since
16 we have a transcriptionist here.

17 DR. FEIGAL: David Feigal, I'm the
18 Director of the Center for Devices and
19 Radiological Health.

20 MR. BAKER: Dennis Baker, I'm
21 Associate Commissioner for Regulatory Affairs.

1 DR. BUCHANAN: Bob Buchanan, Science
2 Advisor, Center for Food Safety and Applied
3 Nutrition.

4 DR. WOODCOCK: Janet Woodcock, head of
5 the Center for Drugs.

6 DR. CASCIANO: Dan Casciano, Director,
7 NCTR.

8 DR. BILOU: Andrew Bilou, (ph)
9 representing FDA Center for Veterinary Medicine
10 in the absence of our center director and
11 director of research.

12 DR. LANGER: Thank you very much.

13 I'd like to ask Dr. Schwetz, the
14 Acting Principal Deputy Commissioner of the FDA
15 to make a few introductory remarks.

16 **Introductory Remarks**

17 DR. SCHWETZ: Thank you, Bob.

18 There are a number of things I want to
19 comment about, and this isn't a speech that has
20 a beginning or an end; it's just to give you an
21 idea of some of the administrative things that

1 are going on within the Agency right now that
2 we're hearing; and then more importantly, some
3 of the scientific issues that are in front of
4 us. And they're not necessarily in an order of
5 priority, but I will talk first about the
6 status of the Commissioner.

7 As you know, Dr. Henney's resignation
8 was accepted in January, and they asked me to
9 serve as the Acting Commissioner, so that's
10 been three months ago.

11 A search is ongoing for a
12 commissioner; people have been interviewed, but
13 there isn't anybody who is being prepared, to
14 my knowledge, for a Senate hearing. So as far
15 as I know, the search is still going on, and
16 the interviews of candidates continues. So
17 until then, I stay on as the acting
18 commissioner.

19 From the standpoint of the budget, you
20 may be aware that the president provided his
21 budget to Congress on April 9th, and within all

1 of the federal government, NIH probably did
2 better than anybody or most other parts. But
3 the FDA did quite well, too, in the President's
4 proposed budget we have about a 10 percent
5 increase.

6 So that's better than we've had in
7 past years, and it speaks well for the support
8 of our new secretary and the White House for
9 the FDA needs.

10 The increases within our 2002 budget -
11 - now remind you, this won't be our budget;
12 this is just the President's budget that goes
13 to Congress, and goes to committee for various
14 manipulations from them, but this is at least
15 what the White House has proposed.

16 The increases that we -- the biggest
17 increases that we have in this 2002 budget
18 include mad cow disease, BSE, money for
19 additional work in the area of human subject
20 protection; increased number of infections,
21 increased capability for tracking adverse

1 events, and for the science infrastructure.

2 So a lot of the things that are in the
3 2001 budget are supported at the level they
4 were, but there are a number of areas of
5 emphasis where the increases, really represent
6 or make up that 10 percent.

7 We've had the Huse Appropriations
8 hearing in March, and our Senate Appropriation
9 hearing comes up on May 10th.

10 Another topic, we have formalized an
11 Office for Human Subject Protection within the
12 Office of the Commissioner as the title of the
13 Office for Human Research Trials. We have
14 advertised for an office director, and that
15 will be announced soon. In the meantime, David
16 Lape, from our Center for Drugs, has been
17 serving as the director of this office as we
18 brought it up to speed and got it formally
19 organized.

20 So it again is another effort to bring
21 together the whole agency activities under one

1 office for coordination, not for the actual
2 execution within the Centers, but to make sure
3 that we have a focal point within the Office of
4 the Commissioner for human subject protection
5 kinds of issues.

6 You have undoubtedly heard various
7 thoughts about a single food agency; and some
8 of you are much more closely involved in that
9 series of thoughts than some of the rest of
10 you, but if there is a single food agency that
11 is formed at some point in time, it will
12 obviously have a major impact on the FDA.

13 This was the big topic of discussion
14 last year; it settled off at the end of the
15 administration; it's now coming back up as a
16 topic of more discussion. There are a lot of
17 private interest groups who are pushing for a
18 single food agency. There are a lot of us who
19 are not necessarily convinced that if we went
20 through all of the efforts to come up with a
21 single food agency, that things would work a

1 lot better than they are today. Things are
2 working better today in terms of interagency
3 coordination in the food safety area than they
4 ever have before. And it's because of the food
5 safety initiative, it's because of the
6 discussions of a single food agency, it's
7 because of some problems that we've had in the
8 food safety area that have brought us together;
9 but for a lot of reasons, we are working as a
10 single food agency, but more closely today than
11 we were even as little as three years ago.

12 So we don't know where this discussion
13 will take the whole area; but if you just think
14 about it a little bit, and there are some 12 to
15 14 different federal agencies that are involved
16 in food safety issues, U.S.D.A., FDA and EPA,
17 CDC are obviously the biggest ones. If this in
18 fact -- we keep pushing that if there's going
19 to be a single food agency, it has to be
20 oriented toward Health, as supposed to
21 supporting cultural or environmental concerns,

1 all of which are important, but we think that
2 if there is going to be a movement toward a
3 single food agency, the primary driving factor
4 has to be protecting human health.

5 So all we can do is wait and see where
6 that goes.

7 Interactions with the Department and
8 the White House, this is the first time that
9 I've had the opportunity to serve in a
10 transition time like this, and there are a lot
11 of things to be learned. And I can't imagine
12 the difficulty of the job of Secretary Thompson
13 coming in from a medium-sized state as a
14 governor where, in his words, he could wake up
15 in the morning with an idea and by afternoon it
16 was not only decided, it was implemented. And
17 here he also says that he can't even write his
18 own speeches, he can't even say his own things,
19 somebody tells him what to say and when to
20 stop.

21 (Laughter)

1 So it's a whole different thing, and
2 as a result, when you've got an agency like
3 ours where things move on a daily basis, on an
4 hourly basis, on a pretty smooth basis, and
5 there isn't a day when there isn't a major
6 issue or a hearing or interviews with the
7 public press, and we're in the newspaper more
8 than most federal agencies, and for the most
9 part it's either information or good; it isn't
10 always bad. There are some other agencies that
11 have a different track record than ours.

12 But to have someone come in and be in
13 charge of the Department and have somebody
14 under you who's in the newspaper every day is a
15 real challenge. So we're working on it, and
16 there are things that we discover every day
17 that are things that -- we tell the Department,
18 we tell them a lot of advanced, and we tell
19 them at the last minute: How do you work with
20 the Department to make sure that things go
21 smoothly from the standpoint of them being

1 involved, but allowing us to keep the machinery
2 going?

3 There are a number of agencies, a
4 number of organizations that say that during a
5 transition like this, they in effect shut down
6 for months, just to rediscover how to work.
7 Well, we obvious haven't done that, and we
8 can't. The number of things that happen if you
9 stop for just a few days, the backlog becomes
10 insurmountable.

11 So we have worked hard to keep things
12 going.

13 Scientific matters. We have worked a
14 lot in the last few years in the area of
15 leveraging, to figure out how to magnify our
16 capability of getting work done by reaching out
17 and having other people help us through one
18 mechanism or another, and I'm not going to go
19 through that list of leveraging activities, but
20 to add a new one.

21 We are currently leveraging with the

1 University of Mississippi Natural Products
2 Research Center to expand the capabilities for
3 doing work on dietary supplements at various
4 levels; analytical work, toxicology work, the
5 use patterns, what might be happening in
6 humans, a large variety of work on dietary
7 supplements.

8 That's an area where we expect
9 information to come out that will be useful to
10 all of us in terms of, how do we move forward
11 in knowing more about dietary supplements and
12 having the public understand better what
13 dietary supplements do and don't do.

14 Mad cow disease. It's probably not
15 inappropriate for a person running the FDA
16 right now to be a veterinarian with some of the
17 things that are going on with mad cow disease
18 and chronic wasting disease in elk, and
19 bioengineered foods and a number of these
20 things that have been part of our past as
21 veterinarians.

1 Two things that the FDA is doing right
2 now about mad cow disease, is trying to keep it
3 out of the U.S. and that's an import issue and
4 the kind of thing that Dennis Baker and our
5 field organization does 24 hours a day, trying
6 to keep things out of the country that might
7 bring mad cow disease into this country.

8 But the other one is the 1997 feed
9 rule that we have that is a Center for
10 Veterinary Medicine rule that says that you
11 can't take ruminant parts and feed them back to
12 ruminants. So we're out there with the states,
13 inspecting every feed mill, every rendering
14 plant, every place where you might have
15 commingling of ruminant, blood, bone meal,
16 nervous tissue of some kind back into cattle
17 feed, trying to be sure that the appropriate
18 records are being kept and if there is
19 commingling, that we go back to that feed mill
20 or that rendering plant wherever this
21 occurring, the blender, to be sure that they've

1 gotten things under control and we don't have
2 ruminant parts being fed back to ruminants.

3 At this point because we don't have a
4 diagnosed case of mad cow disease in this
5 country, it's a difficult spot to be in,
6 because there are cases where there is
7 commingling, and then what do you do with those
8 cattle? Because we haven't had mad cow disease
9 in this country, it's obvious to say that
10 "Well, there isn't a problem for these cattle"
11 but that's where Europe was a decade ago, and
12 they allowed mad cow disease to amplify in
13 their country because they didn't enforce a
14 rule that kept ruminant parts out of animal
15 feed.

16 So there are a lot of things that
17 we're working on with this to show that we
18 don't have mad cow disease coming into this
19 country or that we can prevent its spread if it
20 ever does get here. There are no cases of BSE
21 now, there are no cases of the human

1 counterpart, variant CJD. It's likely that we
2 will see human cases, and not coming from our
3 cattle but we have a lot of people would have
4 spent time in England and other European
5 countries that have mad cow disease, and the
6 possibility that one of them would come back
7 here and be a case of variant CJD is
8 predictable. And at that time I think there is
9 going to be a large nervousness about the
10 safety of our own cattle and the possibility
11 that we again could have it in our cattle and
12 that we would get it in our people of the U.S.
13 from our cattle.

14 Part of the difficulty of this area is
15 that -- it isn't just cattle. The possibility
16 that there are bovine parts in other products
17 is a reality in blood, devices, vaccines,
18 drugs, cosmetics, dietary supplements; so it
19 isn't just a matter of what's in cows, having
20 infected cows. These parts come to our borders
21 all the time, so it's a matter of us knowing

1 what things coming to the borders have and what
2 parts in them that might be coming from a
3 country that is BSE positive.

4 It's a major issue. There isn't one
5 issue that I've spent more time on in the past
6 six months than this one.

7 Consumer confidence in the FDA. Last
8 year there was a survey of five federal
9 regulatory agencies by the Pugh Research
10 Center, the Princeton Research Survey
11 Associates. 28 percent of consumers, 26
12 percent of physicians, 26 percent of industry
13 officials said that they trusted the federal
14 government to do what's right. That doesn't
15 sound much different than being a parent, which
16 isn't very good in terms of your kids thinking
17 that you make right decisions.

18 In fact, 60 to 70 percent said that
19 the government is usually inefficient and
20 wasteful. Let me point out the contrast to
21 what they said about the FDA. 72 to 85 percent

1 trusted the FDA to make the right decision.
2 That put FDA at the top of the charts, with an
3 overall favorable rating of above 80 percent.
4 And that's more than twice the approval rate
5 that the public has for the federal government
6 in general.

7 That's a reputation that I assure you
8 I'm committed to maintain and enhance, because
9 that was hard to come by in these 96 years of
10 the agency, and it's extremely important that
11 we protect that and keep that edge.

12 Let me comment a little bit about
13 biotech issues. Genetically modified foods,
14 animals, as well as plants. Animals, you've
15 seen that we are looking at a salmon that has
16 been genetically modified to have a higher
17 growth hormone level that grows much more
18 rapidly than the non-modified counterpart. The
19 real concern isn't safety; the larger concern
20 is that as these are raised in pens in rivers,
21 in fact whether or not they're all sterile.

1 Because if these escape, then you've got an
2 environmental problem that is of considerable
3 concern to a lot of us. But from the
4 standpoint of whether or not these are safe to
5 eat, that's not -- that's under review, but
6 that isn't the most obvious concern.

7 So that's an example of an animal, of
8 a genetically modified animal that is in front
9 of us.

10 In the area of genetically modified
11 plants, up to this time there are about 50
12 genetically modified foods on the market in the
13 U.S. today, and it's been voluntary that the
14 companies would come to us and say that they
15 are developing this product, here's what it
16 looks like genetically, here's the benefit. It
17 has natural pesticidal activities, or better
18 handling properties or better growth
19 properties, whatever the case might be.

20 The question for the most part with a
21 lot of these genetically-modified foods, is

1 whether or not they are going to be allogenic.
2 Those are the things we look at.

3 We in the last year have said that we
4 don't -- we put out a proposed rule that this
5 should no longer be voluntary. In fact, it
6 should be mandatory that the companies come and
7 talk to us before they would put it on the
8 market.

9 Another thing in that area is that we
10 have put out guidance for label, and that's
11 another major issue as to whether or not these
12 genetically modified foods should be labeled as
13 such, and how can we label them without giving
14 the message that these are safer, or less safe.
15 Neither one of those should be the message that
16 a person would receive if they saw that symbol;
17 they should just be able to know that this has
18 some genetically modified component in it.

19 Half of the processed food that's on
20 the shelf in the grocery store has some
21 component that's genetically modified from this

1 technology, already. So it isn't that this is
2 something that might come some day.

3 Cloning is another issue in this whole
4 biotechnology area; some of you may have seen
5 the articles in the papers recently that say
6 that there are at least two dairy herds in the
7 U.S. that are cloned; one in Wisconsin and one
8 in Massachusetts I think it is. So that
9 technology is here. Also articles in the New
10 York Times and USA Today recently involved
11 cloning units.

12 It's something that we're taking very
13 seriously because of the concerns about the
14 safety. We do have authority to regulate human
15 cloning, and at this point it isn't clear that
16 it can be done without safety concerns to the
17 developing embryo or to the mother. But
18 there's going to be a lot more visibility
19 there.

20 I would just mention a couple of other
21 things, Bob. Sorry, I know I'm going on longer

1 than I thought.

2 DR. LANGER: That's all right.

3 DR. SCHWETZ: When you talk about the
4 sexy and sophisticated things that have to do
5 with gene transfer and genetic modification,
6 it's easy to forget that some of the old
7 problems that have been with us forever, keep
8 haunting us as well. An example there is
9 mercury. Mercury in fish, mercury in vaccines;
10 these are not highly sophisticated issues or
11 problems, but there are some of these old ones
12 that keep coming up as well.

13 And we're very pleased to say that the
14 pressure that we've put on the industry to get
15 rid of thimerosal in vaccines has succeeded in
16 now having all of the vaccines that are
17 routinely given to children up to six months of
18 age can be given with vaccines that either have
19 no ethyl mercury in them, or it's at such a
20 negligible level that it's not a concern. So
21 that's a step in the right direction.

1 In terms of scientific training, this
2 is something that is still of major importance
3 to the agency, recruitment and retention. We
4 have been in a hiring freeze that is typical of
5 every new administration, and that's gradually
6 being lifted, but it isn't lifted fully yet.

7 We're going to talk this afternoon
8 about the FDA University, so that's something
9 that we will have an opportunity to discuss in
10 more detail, and I'll have some additional
11 comments and thoughts about some things I'm
12 thinking about when that comes up.

13 Bob, I'll turn it back to you. If you
14 want to take time for questions or we can do it
15 later.

16 DR. LANGER: Are there any questions
17 that anyone has?

18 DR. FENNEMA: A comment.

19 DR. LANGER: Yes.

20 DR. FENNEMA: This is an advisory
21 committee, so I would like to offer a bit of

1 advice. And this concerns your relationships
2 with your new boss, Tommy Thompson, former
3 governor of my State of Wisconsin.

4 The advice is this: Just make
5 absolutely sure he never runs out of gasoline
6 for his Harley-Davidson motorcycle.

7 (Laughter)

8 DR. LANGER: Thanks.

9 I think with that, I'll turn it over
10 to Liz Jacobson, who's going to give you an
11 update on action items from the November 2000
12 meeting.

13 Liz?

14 **Update on Action Items**

15 DR. JACOBSON: Thanks, Bob.

16 I just wanted to spend a couple
17 minutes updating you on where we are with the
18 action items that came out of the November
19 Science Board meeting. This is a part of the
20 agenda that I know Bob is particularly
21 interested in having every time we meet.

1 We didn't have many action items from
2 the last meeting, but the ones we did have were
3 quite substantive. First, as you remember, at
4 the last meeting we presented an overview of
5 the emerging scientific issues that we're
6 facing at FDA, combined with our resource
7 constraints. And the Board acknowledged the
8 kind of grim situation we're in, which for the
9 2002 looks like it may be improving a little
10 bit.

11 You also urged us to pursue innovative
12 methods to get our work done, including
13 partnering and leveraging and collaborating
14 with outside groups, particularly with the
15 National Science Foundation. And with Dr.
16 Cowell being on the Board and being very
17 supportive and helpful for us, we've been able
18 to follow up with NSF and I wanted to tell you
19 a couple of things we've done.

20 We've had several meetings with the
21 engineering directorate to talk about

1 partnering opportunities; and in March we met
2 and drafted a draft memorandum of agreement
3 describing a pilot collaboration. And this is
4 a joint effort, it's very broadly written at
5 this point to allow both hands-on research as
6 well as workshops and colloquia in areas of
7 leading edge technology. And the idea is to
8 underpin both NSF's and FDA's efforts with
9 respect to pioneering biomedical technologies.

10 So both staffs, both from FDA and NSF
11 are pretty happy with the draft agreement that
12 we've got, and we're hoping to have it
13 finalized in a month or two.

14 The FDA Center for Devices and
15 Radiological Health and NSF's Division of
16 Bioengineering and Environmental Systems have
17 already been collaborating in the field of home
18 care technologies, particularly trying to care
19 for the kinds of medical devices that might end
20 up in the home environment, and we have worked
21 together on one workshop, and they're in the

1 planning stages for another. So that's working
2 well.

3 Then we have a number of other
4 projects, much less developed in scoped out
5 with NSF; I'll just mention a couple of them.

6 We're looking to do something called a
7 "scientists in residence" program. It might
8 end up being called up something else, but
9 that's our name for right now, which would
10 allow exchanges between FDA and academic
11 scientists in a type of sabbatical program.
12 And also a science literacy program that would
13 be aimed at helping students understand and
14 appreciate the new discoveries in science that
15 are going to impact their futures, many of
16 which will be regulated by FDA. And the goal
17 is to help make kids more science literate,
18 much like we try to make them computer
19 literate.

20 I'd just like to point out that our
21 Center for Food Safety and Applied Nutrition

1 already has such an effort underway, a very
2 nice effort developed called science in our
3 food supply. They work together with the
4 National Science Teachers Association and
5 developed a program for middle and high
6 schoolers that helps them develop safe food
7 handling techniques and enhances their
8 knowledge about food safety.

9 And the final initiative is a broader
10 collaborative workshops program that would
11 enable jointly sponsored workshops by NSF and
12 FDA on new technologies. And we've already
13 begun discussions of having a workshop that
14 would focus on genomics and proteomics.

15 So there's a lot of activities
16 underway, and we're looking forward to these
17 collaborations; I think they're going to be
18 wonderful.

19 And we also have an effort underway
20 with the Department of Defense. We're talking
21 to DoD on also a memorandum of understanding,

1 formalizing an agreement between CDRH and the
2 Telemedicine and Advanced Technology Research
3 Center at Fort Deitrich, to collaborate on
4 scientific investigations. And here we're
5 going to be looking at measurement methods and
6 laboratory evaluation techniques on leading
7 edge technologies.

8 Another thing I wanted to -- another
9 recommendation we got from the Board last year
10 was that we should be supporting research from
11 the Commissioner's office with seed money, and
12 I said "Well, I didn't have any, but that I was
13 going to ask for some," and you all said "Well,
14 you didn't ask for enough."

15 But we are doing that. The Office of
16 Science Coordination and Communication got
17 funds from the commissioner to the tune of
18 \$500,000 to fund some seed projects for this
19 coming year. And we met yesterday. We had --
20 I know it isn't a lot of money, but we had
21 intense interest across the agency. We got 98

1 concept papers for that money, and we asked for
2 22 of them to be developed into full-blown
3 proposals, and we met yesterday to look over
4 those proposals, and we have six that we think
5 we can fund at least partially; and we're going
6 to look for funding for a few of the others.

7 So again, it's not a great deal of
8 money, but it has spurred a lot of interest.
9 Bern is sitting right here, so I'll say that we
10 intend to ask for more money next year.

11 The final action item that we had was
12 to report back to you on the status of our
13 programmatic peer review for the Center for
14 Devices and Radiological Health, and Dr. Feigal
15 is actually next on the agenda, so he's going
16 to talk to you about where that effort is; and
17 we're also asking Dennis Baker, who is our
18 Associate Commissioner for Regulatory Affairs,
19 to brief you today on the field activities.
20 What our Office of Regulatory Affairs is doing
21 to get their science review underway; they're

1 just starting this process, and I think you'll
2 find that very interesting, too.

3 So I think that was actually the list
4 of items. As I said, it wasn't a long list,
5 but they were important.

6 DR. LANGER: Yes.

7 DR. DAVIS: The six that you expect to
8 fund at least partially, where will the balance
9 of that money come from, assuming you fund
10 partially six, do they go back to individual
11 agencies to try to compete for the balance of
12 that money?

13 DR. LIZ JACOBSON: No; good question.
14 I also forgot to mention, as soon as we get the
15 final sheet typed up, I'll send it to all of
16 you so you'll see what kinds of projects were
17 in the competition.

18 With the money that we have, we can
19 fund four of the projects completely. Two of
20 them we're asking them to go back, we think
21 that there are some leveraging opportunities

1 that look obvious to us, and we're asking those
2 other two projects to do that.

3 And then we have sort of an approved-
4 but-not-funded list that we're going to be
5 looking around for other opportunities, either
6 within the agency or maybe even outside the
7 agency.

8 DR. LANGER: Are there any other
9 questions?

10 DR. FENNEMA: I have one.

11 You didn't mention -- I may have been
12 distracted a moment -- the Doris Hare testimony
13 from the last meeting?

14 DR. LIZ JACOBSON: Yes. I didn't
15 mention it because it isn't quite finished.
16 The Board was given the full comments from Ms.
17 Hare, and also information from the agency on
18 what we had done that we felt was relevant to
19 the topics that she was raising. And that's
20 been circulated to the Board and we're sort of
21 waiting to hear back from the Board what your

1 reactions were to what we presented; and that
2 would be summarized in a written statement that
3 Bob would then send to the commissioner.

4 DR. LANGER: There was something sent
5 to everybody, should have been at least a month
6 ago, and I followed that up with an e-mail a
7 few days ago, which some people have already
8 gotten back to me on. Others -- you know, it
9 depends on how often people check their e-mail,
10 probably.

11 I would be a bad reference point in
12 terms of -- but you should have something.

13 DR. FENNEMA: Well, I would like to
14 comment about that, because I read the FDA
15 response to this. And it would seem
16 inappropriate, in my judgment for this
17 committee to respond directly to Doris Hare
18 unless we felt that FDA's response was
19 inappropriate and inadequate.

20 I felt, after reading Janet Woodcock's
21 letter, that that was handled quite well, and

1 it would be my recommendation that this Board
2 would simply endorse what FDA has done.

3 DR. LANGER: Well, that's basically
4 what was done. But you'll see that in the e-
5 mails. But my feeling is I want to get
6 everybody's comments; I've gotten I think three
7 back so far. And anything that people want to
8 say, we want to just do the best we can.

9 Yes, Harold.

10 DR. DAVIS: Well, I haven't seen the
11 e-mail; I've been traveling. But I agree with
12 Owen. Even when it was put in court as we
13 ought to respond, I felt a little -- that that
14 wasn't our right to respond directly to her;
15 and I read the package, and I thought it was
16 very well handled.

17 DR. LANGER: Well, it sounds to me
18 like we're pretty much of a consensus, both
19 from that and the e-mail responses I've
20 received. But we'll deal with that formally.

21 Good. Thank you both.

1 Do you want to make introductions, or
2 shall I?

3 DR. JACOBSON: Well, David Feigal, who
4 is the Director of our Center for Devices and
5 Radiological Health, is going to talk about
6 where CDRH is in their science review, and
7 he'll be followed by Dennis Baker, talking
8 about the ORA Science Review.

9 **Update on Science Review**

10 [Slide]

11 DR. FEIGAL: You probably all wondered
12 how we review high technology. This is a slide
13 from the New York -- a little bit earlier, the
14 guys holding the two devices up and saying
15 "Well, your chip looks a lot like their chip."
16 And that's the first step in the process, but
17 it's a little more complicated than that.

18 That's what we'd like to share with
19 you as we do the review of our science
20 programs.

21 Let me just recap briefly some of the

1 things that I presented last time and gave you
2 an update and some of the progress we've made
3 since that time.

4 The purpose of the science review for
5 us is to really showcase and to share the
6 vision of how we use science in a day-to-day
7 fashion as we look to accomplish our mission to
8 promote and protect the public health by
9 ensuring the safety and effectiveness of
10 medical devices and the safety of radiological
11 products.

12 As you know, last time I talked a
13 little bit about how often we are characterized
14 as having premarket programs and postmarket
15 programs, but that we've developed a way of
16 looking at our products that really emphasizes
17 working with the entire life-cycle of the
18 product from the time that it's a concept and
19 then a prototype to a product which has
20 preclinical or performance testing, and
21 clinical information if that's required for

1 that type of product; the types of
2 manufacturing scale-up and marketing,
3 commercial use, obsolescence, and in fact it's
4 a pipeline, and it's a multi-generational
5 pipeline.

6 One of the things that makes devices
7 both interesting and challenging is the fact in
8 many product areas, a given product will remain
9 on the market six months, twelve months,
10 eighteen months before it's replaced by the
11 next generation of that product. And that's a
12 very different way of thinking about products;
13 you have to organize the way that you collect
14 evidence, that you look at evidence, compared
15 to a well-patent-protected pharmaceutical that
16 may be on the market for many, many years with
17 not very many modifications.

18 [Slide]

19 If you took the life-cycle of the
20 product, there is a regulatory framework that
21 you can place around the product. Early on,

1 they are the issues about "Whose product is
2 this?" And there's a process of asking for
3 designation of about, is this a device, is this
4 a biologic, is this a drug?

5 There are interactive processes that
6 we have, we actually average about two meetings
7 per business day with companies about products.
8 We often discussion investigational device
9 exemptions, the device equivalent of an IND for
10 a drug.

11 As time goes on, the regulatory
12 process becomes more structured as we move
13 toward applications for marketing approval,
14 advisory panels, and then when the product is
15 out on the market, we have the regulatory
16 mechanisms that begin with the inspections that
17 typically occur about this time and then
18 postmarket information that comes in. If the
19 product has problems there may be safety
20 alerts, there may be recalls or other types of
21 issues.

1 So when you frame the kinds of
2 challenges that we have around the whole life-
3 cycle you get a much richer way of looking at
4 our regulatory task, and you realize that
5 there's a lot of information; the reason for
6 all the connected lines is that it's possible,
7 particularly in a multi-generational product,
8 for one part of the life-cycle to inform all
9 the others.

10 The other way of organizing the
11 concept of the life-cycle is to look at the
12 scientific disciplines and actually other
13 disciplines go along the life-cycle are in more
14 than one place, but they have been put close to
15 areas where there is plenty of action, so early
16 in the product life-cycle, you're evaluating
17 issues such as biocompatibility or toxicology
18 if it's an implant, for example. If it's a
19 product with clinical studies, there is the
20 scientific machinery about clinical trials in
21 designing and evaluating that evidence; there

1 are all the issues around evaluating
2 manufacturing quality and quality systems and
3 methods.

4 In the period where the product is in
5 use, you have the opportunity to evaluate
6 events and see what you're learning from the
7 product from isolated events or recovered
8 devices that have failed, other types of
9 issues.

10 [Slide]

11 So if we wanted to characterize our
12 vision of how we operate and how we do our
13 business, is that we ensure the health of the
14 public throughout the total product life-cycle,
15 and it's everybody's business; it's something
16 that we can't do just by ourself there; there's
17 a responsibility for the manufacturer, there is
18 a role that -- an important role that health
19 care providers play. And increasingly with
20 self-care, there's a role for consumers.

21 So what we wanted to do was to arrange

1 a review of the way that we use science in the
2 Center. This is different than the previous
3 program reviews which focused on the research
4 efforts of the Center. We in fact wanted to --
5 you used the words good services, and to use an
6 outside peer review, not just to focus on our
7 research efforts, which might be 10 to 15
8 percent of our budget, but instead to look at
9 the way that science is embedded and
10 interwoven, and whether or not it's adequate
11 for the tasks that we have throughout the life-
12 cycle.

13 So the framework is that we developed
14 an internal review by CDRH staff, and I'll show
15 you where we are with that, and then we're
16 preparing for an external review by non-FDA
17 staff, by the external review panel; and that
18 committee was nominated from academia, from
19 trade associations, from other government
20 agencies, from some members of this Board. And
21 we have organized a panel from industry that

1 the external review board will be able to
2 interact with and hear from that point of view
3 about how we are doing.

4 The review seeks information about the
5 Center's decision-making process. The
6 fundamental thing that FDA does, and the thing
7 that we actually get on the hot seat for
8 occasionally, is to make regulatory decisions.
9 When we're just thinking about things and don't
10 have a decision to make, people aren't terribly
11 concerned about things; but if they're waiting
12 for us to do things, then they're waiting for
13 us to make a decision. It's a science-based,
14 it's an evidence-based decision; it's one that,
15 as Dr. Schwetz mentioned, the public has great
16 confidence in. I think that's in part because
17 they feel that there's a high level of
18 scrutiny.

19 We're going to look at the impact of
20 the decision making, of the resources required
21 to do the kinds of scientific work we do, and

1 the integration of the way that the decisions
2 are made throughout the regulatory process.

3 Are there ways to provide feedback
4 mechanisms and to document decisions and to
5 enhance the way that our organization learns
6 from the products that we review and are
7 involved with.

8 And we would like to be critiqued on
9 our preparedness for addressing future
10 scientific challenges.

11 [Slide]

12 This is a snapshot that I showed you
13 last time of part of the process. We put
14 together about a year and a half ago now,
15 almost two years ago, a science review working
16 group that began working these issues with us
17 and the senior leadership, management. At
18 about the same time we were also beginning to
19 work on a strategic plan for the center.

20 We put together an internal sciences
21 review group and they have been preparing an

1 internal review document. Much of that process
2 is well underway and this document will be
3 available for the external review group when
4 they meet this summer.

5 I presented the outline of that to you
6 last time; let me just again remind you what
7 that is and tell you some of the details of how
8 we did some of the things.

9 There will be resources for this
10 review process. One of them will be the
11 science review team. Because we wanted to
12 showcase the way that we use science throughout
13 the product area, and because we have such a
14 breadth of products, we chose to take part of
15 the review and focus it on one class of
16 reviews, electrical stimulators.

17 So we will make available and continue
18 to utilize the scientific review team which has
19 particular expertise in the Center, across the
20 Center in this area.

21 The Internal Review Committee

1 developed a protocol for describing in detail
2 how we've dealt with the scientific regulatory
3 issues at different parts of the life-cycle and
4 developed this across the Center, and did this
5 in preparation of part of the document.

6 As part of the process, you remember
7 we made this presentation to you in late
8 October or November; when we organized the
9 internal review group and they began work in
10 earnest in late February and began the process
11 of putting together the internal review.

12 The parameters, we are looking back at
13 a five year historical period. It's a little
14 bit easier for us to work with many of the
15 decisions that are already complete because
16 those are often public records or records that
17 can be discussed; and there's the ability to
18 have things that have been fully developed.

19 Our intent is not to really focus on
20 the process, but some of that will be necessary
21 to look at how it relates to the way that we

1 use science in decision-making.

2 There was some concern on our staff
3 that this would be a retrospective second-
4 guessing of how good were our decisions, and
5 that's not the intent, either. The intent
6 there is to really look at the way the science
7 was used in the decision-making. As you look
8 back, you will probably see that there were
9 some close calls, there are some things in
10 hindsight that could be better answered now
11 with what we know now, but that would not be
12 the purpose. The purpose is to really look and
13 see how we use science.

14 [Slide]

15 The table of contents of the report
16 that the external committee will have will have
17 this structure; and in the background, there
18 will be a description of each of our offices;
19 that's our next large organizational unit under
20 the Center.

21 Each office will describe the flow of

1 information into that office, how the issues
2 are identified, how science is used in the
3 programs and functions, how scientific
4 decision-making is made in the Office of Device
5 Evaluation, for example, which has products
6 early in their life-cycle, or in the Office of
7 Biometrics and Surveillance, which has our
8 postmarket surveillance programs.

9 We're going to look at the impact that
10 scientific decisions makes. We have had a lot
11 of discussions about, how do we know that we're
12 really adding value with where we apply
13 science, and that it has impact on the public
14 health and that we're not simply tracking our
15 process but in fact we're self-aware of the
16 impact of our science.

17 We will provide you a critique and our
18 assessment of the kind of expertise needed.
19 There's the internal access of our own staff,
20 there's external from our consultants, from our
21 advisory committees, from our leveraging

1 collaborations, from our other mechanisms. We
2 will assess for you where we think we have
3 strengths, where we think we have gaps.

4 We will identify how the offices
5 interact with other offices and the impact of
6 not sharing the information in this
7 information-rich process. And we'll look at
8 the infrastructure needed to accomplish
9 decision-making and how the office positions
10 itself for the future.

11 So this will be presented as
12 background, and as a way of illustrating how
13 science really fits in with the total product
14 life-cycle. Again, a basic paradigm that this
15 is science-based regulation, looking at the
16 scientific roles, looking at the domains, and
17 identifying what the scientific work is.

18 The area that we've chosen to provide
19 focus on, and this allows us to ask for
20 committee members, many of whom have expertise
21 in this area, is to pick an area that is

1 illustrative of the way that we use science.
2 And so we will be prepared to essentially tell
3 the committee anything that they want to know
4 about this area. But in our document, we will
5 actually pick some highlighted cases that we
6 think illustrates this, and I'll talk a little
7 bit about how that works with the external.

8 We'll also address some of the
9 specific issues: How we peer review both the
10 regulatory process, how we peer review our
11 research projects, how we prioritize and select
12 projects. The issue that's beginning to emerge
13 as GAO is getting ready to release the planning
14 funds for White Oak, we are going to have to
15 rebuild our labs, our organization from the
16 ground up; and that's both a challenge and an
17 opportunity.

18 And we have equipment challenges that
19 this board's been made aware of; ours are no
20 different than the other Centers.

21 We will provide a current situation

1 analysis, we will provide an overview of what
2 we think are the internal strengths and
3 weaknesses, what we think the external threats
4 and opportunities are. What do we do well and
5 are improving, or where do we have gaps and are
6 falling behind. And where to present, in a
7 brief form, the strategic vision and the types
8 of tools we think that we can use to address
9 problems that we identify and problems that the
10 external panel recommends that we address as
11 well.

12 [Slide]

13 So if you go back to this diagram,
14 we'll have the internal document. That will be
15 provided to the External Science Review Group
16 as they meet and convene June 21st. And
17 apologies to Dr. Nerem, this picture was on the
18 web, and as I was scrounging around trying to
19 find his exact title, I also cut and pasted a
20 picture -- and let that be a warning to any of
21 the rest of you, that have pictures up there.

1 DR. NEREM: I hope your web site's
2 secure.

3 (Laughter)

4 DR. FEIGAL: That's right, you need a
5 better firewall on your web site.

6 Dr. Nerem has agreed to chair the
7 committee. We have actually the full
8 nominations for the committee, and I have that
9 information available. We're actually in the
10 process of going through the SGE process and
11 all of that.

12 I have not put on a slide the
13 composition of the committee, because it won't
14 be final until we get through that process.

15 But I wanted to share with you our
16 thoughts at this time of how we're organized,
17 and support the external science review.

18 We're having an organizational meeting
19 in June. And at this meeting, a one-day
20 meeting, we will provide internal review
21 documents and we'll go over the interactive

1 review assignments, and I'll tell you a little
2 bit about how we're going to do that.

3 Then in July there'll be an onsite
4 CDRH site visit, and the first day we'll focus
5 on the early life-cycle, we'll actually do that
6 part of the review, at our Twinbrook facilities
7 where we have our laboratory programs.

8 The second day we will focus on the
9 mid-life-cycle at Corporate Boulevard where we
10 have the majority of that building or staff
11 working with the premarket approval process,
12 the Office of Device Evaluation.

13 And then on Day three, we'll work on
14 one of the facilities that works late in the
15 life-cycle; and there will be an opportunity to
16 meet and work with the staff in the different
17 parts in the Center as we support this.

18 Well, what do I mean by interactive
19 assignments? There is a process in internal
20 medicine -- actually, the surgeons have it as
21 well -- of putting visitors on the spot.

1 Typically what's done is you present them part
2 of a case and then you ask them to discuss it.
3 And the reason they're on the spot is because
4 you don't give them all the information; you
5 want to see how well they do with partial
6 information.

7 [Slide]

8 There's one of these published every
9 week in the New England Journal called Clinical
10 Pathological Correlations. The surgeons often
11 call theirs morbidity-mortality reviews.

12 But what we felt would be interesting
13 would be to ask the committee in some sense to
14 do part of the review wearing our shoes.
15 Trying to see what it would be like to have to
16 make the kinds of decisions that we make.

17 One of these that's very familiar is
18 the middle one, because we're doing that today,
19 it's advisory panels; although advisory panels
20 that are product-specific have a little
21 different focus than this committee.

1 One of the things that we will do at
2 the organizational meeting is that we will
3 provide a background material for an advisory-
4 committee-type decision to the Advisory Panel;
5 and part of the second day, we'll actually be
6 looking at what kind of scientific machinery
7 and expertise it takes to get to that stage.
8 That's a very public part of our operations;
9 it's one that often gets us in the press and a
10 fair amount of public attention.

11 So this one is fairly familiar. We
12 will do this on an issue that, as in a CPC, we
13 know the punch line, we know how the product
14 came out, we will go over this. But we want
15 the committee to have a feeling for the
16 decision-making; and the emphasis is really on
17 how do we use science in making decisions and
18 how does this happen at this point?

19 [Slide]

20 On the first day we do something early
21 in the life-cycle. As I mentioned, we have two

1 meetings a day, on average, with companies; and
2 they're typically labeled "pre-IDE
3 consultations." These are the early meetings
4 where companies that are talking about "How do
5 I develop a product? What are the issues?
6 What are the things that I need to do?"

7 And so one of the things we will do at
8 the kickoff meeting again is to provide a
9 concise case. We will ask the committee to sit
10 in our shoes and to interact with us, one with
11 the company, and we'll say "All right, we've
12 got a new product. These are all our
13 questions. What do we have to do for
14 biocompatibility? What do we have to do for
15 the clinical trials? How much animal work do
16 we have to do before we can get into human
17 trials? When is it safe to do first --?"
18 Those types of issues.

19 And we'll do these in a way that we
20 can talk about the process as we go through it,
21 by using a real case, I think we'll be able to

1 make these come to life a little bit more.

2 Then finally on the third day, when
3 we're focusing on late in the life-cycle, we'll
4 actually ask the -- we'll give the committee
5 some background on a product that's having
6 problems and that we need to write a safety
7 alert for health professionals for.

8 And we'll actually convene them; we
9 call these our ad hoc committees, they're drawn
10 across the whole center, across all the
11 disciplines, and we're looking for what kinds
12 of sciences are needed in that kind of a
13 setting? When to evaluate the events that
14 occur, but secondly to think about all of the
15 sciences of communication, of risk, of dealing
16 with risk; and again put the committee a little
17 bit in our shoes.

18 The other part of the interactive
19 assignment is that we will make available, as I
20 mentioned, people from industry who have worked
21 with products that we've approved in this area;

1 and the committee will have time when they can
2 -- the organization meeting we'll discuss with
3 them what their preference is for doing this.
4 But how they would like to interview industry
5 about, their impressions about how the process
6 scientifically worked.

7 Then the final interactive thing is we
8 will put ourselves on the spot. In this area
9 where we've taken five years of all the
10 products in an area, we'll develop a listing of
11 all the regulatory and scientific work in that
12 area during that five year period, and we will
13 invite the committee, in the time between the
14 organization meeting and when they arrive, to
15 list things they wish to see. If they wish to
16 see our review of a particular study protocol;
17 if they would like to see our review of an
18 application; if they would like to see an
19 evaluation of a safety problem; if they would
20 like to see the adverse reports.

21 Because the committee will be special

1 government employees and will be able to work
2 with confidential documents, we'll actually
3 invite the committee to ask for and to look at
4 anything they want in this product area --
5 because if we just presented the cases that
6 we've chosen, we would worry ourselves that
7 we'd put our best foot forward.

8 And we'll work with the committee on
9 how to do this. They will notify us, when they
10 come on the first day is much the way we do
11 audits; sort of putting ourselves in our own
12 situation, we go to a company and when we
13 arrive, we tell them what records we want to
14 see. And we will invite the committee to do
15 that to us. And we'll make staff available to
16 go over things, and there may be some things
17 that are better explained verbally than you can
18 decipher from the databases and other kinds of
19 systems.

20 But basically in this area, we would
21 like to show you what we've got, and anything

1 the committee is curious about in this area
2 where they have expertise, we'll show them.

3 So finally we will end up with the
4 external science review group, we'll have an
5 external moving document; they'll present that,
6 we think probably in the fall to this group,
7 and they will probably have recommendations to
8 you for recommendations to us, and you will
9 have recommendations and we will work through
10 that process.

11 We are very engaged with this process.
12 I would say that they're probably in different
13 levels of effort have been well over a hundred
14 people in the Center that have contributed and
15 worked and brought to this process.

16 Again, our hope is that we really will
17 show you broadly what it takes, why science is
18 necessary in the processes we do, and invite
19 you to identify what you think our challenges
20 and problems are. You're also welcome to
21 compliment us on things we do well -- and this

1 is to be an exercise really where we learn from
2 an outside group. We are trying to be
3 self-critical with our own internal report.
4 There has been great benefit from even doing
5 that process, and we look forward to working
6 with the committee this summer, and thank Dr.
7 Nerem for his willingness to chair it.

8 So with that, let me stop and see if
9 we have questions.

10 DR. LANGER: Questions?

11 DR. DOYLE: David, with the wealth of
12 experience that the agency has, and review of
13 new devices and the like, is the agency
14 considering developing a computer program that
15 would put all this information into the
16 computer and assist them in making these
17 regulatory decisions?

18 DR. FEIGAL: There have been a lot of
19 proposals like that. It would be nice to
20 report that we had a lot of progress; but Greg
21 Burke, some of you may know, who is the

1 Division Director of Oncology, had proposed a
2 self-reviewing safety section for drugs some
3 years ago, because the way you collect safety
4 information across products is much more
5 similar than effectiveness; and he felt that
6 "Well, if you just organize the data in" -- he
7 was even thinking in those days of just on a
8 spreadsheet, you could write macros that would
9 generate some standard tables and would
10 calculate rates all the same way, and the
11 reviewers wouldn't have to start so much from
12 scratch each time going over safety reports
13 done somewhat differently.

14 I think that -- you know, our steps of
15 getting to the computer is to make some of our
16 processes work without a computer first; and
17 part of that I think has been a large effort in
18 all the centers over the last decade to provide
19 much more guidance about how to submit
20 applications to get the quality of applications
21 so that they're more reviewable.

1 We have gone through, particularly in
2 the Center for Drugs and Biologics, the first
3 generation of computerized applications that
4 come in. And we've learned that just being
5 paperless doesn't necessarily make them easier
6 to review. May make them much bigger. It's
7 often easier to submit a giant computer file
8 than it is to send all of that paper.

9 So I think we're running them
10 together, but we're very interested in the
11 kinds of things that you mention. We do not
12 have much that's there yet.

13 DR. LANGER: Ed and then Kathy.

14 DR. SCOLNICK: David, I first of all
15 applaud your efforts for doing this. I think
16 that having a good review internally and
17 externally of any system is a healthy thing to
18 do; and to do it actually on a regular basis,
19 not just once at the urging of a science board.

20 But I'd like to make a few comments. I
21 think the review that you set forth, there are

1 two aspects to reviewing any organization and
2 how it works. One is the process that uses to
3 review the content that it gets, and to the
4 content of what it comes up with when it does
5 the reviews.

6 You referred to the CPCs that are in
7 the New England Journal. I grew up in that
8 atmosphere, in that town where it's published;
9 and as part of my medical training we had
10 something called Allen Street Rounds, in which
11 residents and interns who took care of patients
12 before Medicare on public wards, were reviewed
13 regularly by the chief resident and had to
14 defend the decisions they made.

15 And I think that as part of the
16 review, I would be interested in several
17 things. One, I as a Science Advisory Board
18 committee member, would really like to
19 understand your peer review process, and that
20 of the entire agency. I think it is a critical
21 component of quality.

1 No one would argue that science is not
2 necessary to review both devices and drugs.
3 It's obvious that it's necessary. The question
4 is the quality of the science that's brought to
5 bear on the process. And the peer review
6 system that you use is critical to maintaining
7 the quality of that process.

8 The second thing I would say is,
9 you've excluded from the review something that
10 I never excluded in any review I've ever had of
11 any organization that I've been in charge of
12 for my entire life.

13 I think that as we did in Allen Street
14 rounds at Mass General, you should have your
15 Center put forward in the documents for this
16 group what you think are the ten best decisions
17 you've made in the last five years; the ten
18 worst decisions you've made in the last five
19 years; the ten most controversial decisions
20 that you've made in the last five years, et
21 cetera, in a self-critical way that opens up

1 what the group has done, where you have been
2 criticized the most, whether that is justified
3 or not and allow the committee to get into that
4 process, et cetera.

5 I think that is the level of openness
6 you need in the review process in order to
7 eventually end up with a strong organization
8 that can really do an absolutely first rate job
9 in the public limelight for reviewing devices
10 and radiological safety. And I'm not sure all
11 of that's really included here.

12 DR. FEIGAL: The peer review is,
13 although it may not be evident from the way
14 that I've laid out the outline and so forth.
15 But I think your suggestions about actually
16 tackling some of the controversial areas and
17 identifying what we think are good and tough
18 and controversial decisions is a very good
19 suggestion.

20 One of the advantages of our
21 presenting this to you and one of the reasons

1 we want to have an organizational meeting with
2 the external review -- before we invite them in
3 for the review itself is so that we can tailor
4 the review and add things and take advantage of
5 suggestions. So those are welcome.

6 DR. SCOLNICK: In terms of
7 interviewing industry, I would encourage you to
8 let them interview your clients in a sense,
9 then across the board in the categories of
10 decisions that I've alluded to, or other kinds
11 of categories like that so that the external
12 committee gets a full view of all the various
13 views and when they have enough information,
14 can begin to understand as you put it, the
15 process for decision-making.

16 And then participate with you in
17 helping come up with constructive suggestions
18 of how to continually improve the process.

19 DR. FEIGAL: Thank you for the
20 comment.

21 DR. NEREM: I'd like to comment on

1 that. I like your suggestions, Ed. It may be
2 that in selecting people from industry to be
3 interviewed by this committee, that in fact it
4 ought to come from the ten best/ten worst, ten
5 most controversial -- I'm not sure if there's
6 another category. Ten most difficult, which
7 may turn out not to have been a controversial
8 decision, but was considered a most difficult
9 decision. So you might think about that,
10 David, in terms of how to select the --.

11 DR. LANGER: I think that's excellent.
12 When you get together in your June meeting, is
13 that going to be a topic for discussion, or
14 will that be prior to the June?

15 DR. FEIGAL: We can address that
16 beforehand. Actually, if I'd asked the people
17 involved in the science review process to stand
18 up, it would be about a third of the room. So
19 you have the audience here to hear your
20 comments and suggestions. We do value them.

21 DR. LANGER: Excellent points.

1 Kathy?

2 DR. ZOON: Just a brief comment to Dr.
3 Doyle's question with regard to review and
4 documentation, consistency of reviews.

5 Part of an effort that we started
6 several years ago which is still ongoing
7 because of its massiveness is basically looking
8 at good review practices. And that's currently
9 underway with the Centers for Drugs and
10 Biologics, acting as a team looking at criteria
11 for reviewing INDs, license applications and
12 other aspects of the review process so that
13 you're not working on one reviewer's
14 institutional memory, but you're actually
15 providing an in-depth analysis to what to look
16 for.

17 In addition, there's an emphasis on
18 looking in the future into doing more template
19 analysis and reviews, where certain categories
20 are considered as part of a standardized review
21 process. And while all of this is good and

1 we're moving forward in that area, I think the
2 issue of getting people to continue to think is
3 extremely important.

4 Because something is written in the
5 document or some template is there doesn't mean
6 everything has been addressed; and a case in
7 point just to emphasize this point would be in
8 the area of gene therapy where we essentially
9 had guidances, standard SOPs on how to review
10 these.

11 Then in the context of our
12 investigation following the death of Jesse
13 Gelsinger, we found out that areas of the
14 science had evolved information over the past
15 five years which had been in the guidance
16 documents certainly needed to be updated and to
17 be re-thought in how that information was
18 requested and the quality and the types of
19 questions that were being asked.

20 So a couple of lessons learned from
21 this is, while all these guidances and

1 templates and good practices are essential to
2 an organization, really critical thinking is
3 essential in the FDA in order to assure product
4 safety and moving products along; and it goes
5 to the very heart of this board and what you're
6 trying to help us with is really developing the
7 esprit de corps of the scientific staff to be
8 able to do that. And it's a critical element.

9 DR. SCOLNICK: Also, picking up,
10 David, on your comment about science and the
11 fundamental importance of that to your review
12 process, we all know science is global; it's
13 one of the wonderful things about the field or
14 the discipline. And I think that one other
15 aspect of the review that you might consider,
16 it's a little bit harder to do, but to give the
17 board that you're engaging some feeling for the
18 review process in other sophisticated countries
19 for devices and radiologic health.

20 The U.S. is a leader in science; we're
21 also not the only country that does science,

1 we're not the only country that does device
2 reviews. And most people brought in to review
3 a situation like this will be lacking in
4 knowledge of what other sophisticated --
5 sophisticated countries that have the same
6 goals as the U.S. FDA does in their review
7 processes and what can be learned from them.

8 If you're really going to do it, do it
9 in depth in a way that people can really get a
10 feeling for it and make constructive comments.

11 DR. FEIGAL: Thanks for the comment.

12 I think one of the things that we again will
13 work out with the committee when we meet with
14 them is what types of things they would like
15 that would make the best use of our interacting
16 and their actually being on site, what types of
17 materials would they like as background, and
18 what we'd like to have as written material,
19 opportunities to discuss that.

20 So again we will certainly address
21 that, and I think we'll work with the committee

1 to see how they want to integrate that into
2 their recommendations and assessment of us.

3 DR. NEREM: And David, am I correct
4 that assuming the person gets approved by
5 whoever approves these things, there will be
6 someone from Canada that's part of the
7 regulatory office that will be on the
8 committee?

9 DR. FEIGAL: Actually on the
10 committee. Beth Peterson will actually be on
11 the committee, will be joining us from Canada.
12 And we certainly know a great deal about the
13 European and Japanese systems, so we can either
14 present those or, if the committee is
15 interested, it's possible for us to arrange
16 video conferences. We actually do that with
17 our regulatory colleagues on a regular basis
18 anyway.

19 But we'll actually have -- my
20 counterpart from Canada on the board,
21 critiquing us.

1 DR. LANGER: Other comments or
2 questions?

3 Before we move on, I wanted to make
4 just a couple more introductions. Rita
5 Colwell, Head of the National Science
6 Foundation and a member of our Board; and from
7 the FDA, Linda Suydam, who is the Senior
8 Associate Commissioner of the FDA, and Kathy
9 Zoon, who is the Director of the Center of
10 Biologics.

11 Just to continue this discussion I
12 want to now turn this over to Dennis Baker, who
13 is the Associate Commissioner for Regulatory
14 Affairs. His office of regulatory affairs is
15 the agency's front line force located in 21
16 districts, and includes 12 field laboratories.
17 And Mr. Baker is going to be giving the Board
18 an overview of the responsibilities of this
19 office and outline his general expectations for
20 an external review.

21 So I think some of the comments we're

1 hearing I'd like to actually continue at the
2 end.

3 MR. BAKER: Yes, we would appreciate
4 it. We are really in our infancy in starting
5 this basic scientific peer review, although we
6 do have a quality management system that we've
7 piloted in the Denver District and we're taking
8 across the country now, which goes hand in hand
9 with scientific review that we've proposed to
10 do across the agency.

11 As you mentioned, ORA is the field
12 component, or sometimes referred to as the law
13 enforcement component of the agency. I do have
14 to tell you, neither term accurately describes
15 what ORA is all about. ORA in its simplest,
16 blends science and law in an effort to protect
17 the consumer. So we're constantly balancing
18 the science needs against what the law says in
19 doing our basic job.

20 [Slide]

21 We are nationwide; we've got some five

1 regional offices; 19 district offices; 137
2 resident inspection posts; 6 Office of Criminal
3 Investigation Field Offices, 4 OCI resident
4 offices, 4 OCI domiciles.

5 In terms of the laboratories as you
6 mention, we actually have 13 laboratories; 5
7 multipurpose laboratories in Seattle, Atlanta,
8 Jefferson, Arkansas, Los Angeles and New York.
9 Then we have eight smaller purpose laboratories
10 where we do some specialty testing; and those
11 are located in San Francisco, Denver, Kansas
12 City, we have a forensic chemistry center in
13 Cincinnati, Detroit, Philadelphia, San Juan,
14 then we have a WEAC facility in Massachusetts.

15 I should also add that we have some
16 partnerships with some states. Minnesota is an
17 example; we have three of our analysts in the
18 Minnesota Department of Agriculture Laboratory;
19 they do microbiological work. The state funds
20 the funds the facilities for us; of course we
21 have to buy our own reagents and so forth for

1 the work that we do.

2 We also have a similar arrangement in
3 L.A.; the Department of Health people in the
4 State of California actually collocate with us
5 in our L.A. facility, and if we're doing joint
6 work there.

7 Then we also have a partnership
8 arrangement with the Florida Department of
9 Agriculture Laboratory and they do quite a bit
10 of work, particularly in the area of dealing
11 with citrus products.

12 This really doesn't adequately tell
13 you about our presence, though, because we're
14 international in scope. As you've all
15 mentioned, we're now in an international arena.
16 We presently cover about 170,000 domestic firms
17 and a couple of hundred thousand foreign firms,
18 and we do this with a total staff of about 3200
19 people.

20 So there's a challenge here, as you
21 might suspect. And as Dr. Schwetz mentioned

1 earlier, we also have to look at the product
2 coming into the country through import
3 channels, and that's working with Customs. So
4 we do a variety of things in evaluating the
5 products coming into the country, make sure
6 they meet our standards.

7 In the midst of all this, we've had
8 quite a management change. As I mentioned last
9 time, we have just about changed the entire
10 management structure of the field in the last
11 couple of years. You're looking at roughly 19
12 districts there, 16 of them have new managers.
13 3 of the 5 regional directors are relatively
14 new.

15 So that's another challenge we've had
16 to deal with in the arena of ORA. Not just the
17 science challenge; we're dealing with gearing
18 up new management as well. That's both good
19 from the standpoint of new blood, new ideas and
20 creativity, but it's a challenge to get them
21 all operating in a uniform and consistent

1 manner.

2 [Slide]

3 So we have broad responsibilities.

4 You're aware of what we cover from the various
5 centers. We want to make sure everything, all
6 our medicines, biologics, medical devices are
7 safe and effective, that we have safe consumer
8 medical radiation products, safe and effective
9 animal drugs, safe wholesome sanitary foods --
10 although looking at that candy and ice cream,
11 I'm not sure about the wholesomeness of the
12 products.

13 (Laughter)

14 We do have an enforcement
15 responsibility to make sure that when we have
16 the people that are not going to comply that we
17 bring them into compliance.

18 [Slide]

19 We can actually segment our program
20 operations into three broad areas; inspections,
21 investigations, lab sciences; which includes

1 our analytical methods development. That's
2 ORA's research arm, developing methods. And in
3 compliance and enforcement activities.

4 I guess basically the best way to
5 summarize this is this is taking a horizontal
6 slice of ORA and taking a look at it. David
7 presented more of a vertical slice; of CDRH in
8 the field we'd have to make more of a
9 horizontal slice to do an evaluation.

10 [Slide]

11 Of course that's what we're going to
12 do. We're going to assess all three areas to
13 make sure that they're functioning as we should
14 do it, basically that we have a fitness for use
15 in all three areas.

16 [Slide]

17 We want to know that field staff
18 conducts and makes determinations and conduct
19 their operations as intended. Basically that's
20 our fitness for use.

21 [Slide]

1 So we're taking a look at this. Usual
2 ORA science-based activities may include just a
3 host of people, but the concept of 'fitness for
4 use' is based on the users and the suppliers of
5 the science agreeing on the level of science
6 needed for decisions ahead of time. And that's
7 a key component here.

8 Generally we would expect that the
9 compliance program covering the area, be it
10 investigatory or analytical, our
11 straightforward compliance would include the
12 information necessary to establish the science
13 expectations of the stakeholders. And other
14 sources of these expectations may be our
15 collection reports, our ad hoc assignment from
16 the centers. Also our inspectors operation
17 manuals, our laboratory procedures manuals.

18 I think perhaps the best way I can
19 explain this idea of fitness for use is in
20 describing a situation where we have product
21 coming into the country that has an unproved

1 pesticide. For the purposes of the law, we
2 would simply need to determine that the
3 pesticide is present.

4 However, some would argue that we
5 really need to quantify the amounts of
6 pesticide so that we can better make a hazard
7 determination for the consumer. This, however,
8 would require methods development and
9 validation, which can take some time and can be
10 quite costly, so how much do we need to get the
11 job done? In essence, to stop the product from
12 coming into the country, what do we need to do?
13 Do we really need to go through all the
14 additional steps?

15 So that's one thing that we constantly
16 have to assess, and it can change from
17 situation to situation. We're constantly
18 looking at what the law requires and what the
19 science available to us tells us.

20 [Slide]

21 We have a number of policy procedure

1 and guidance documents, as you might suspect.
2 We have compliance program, we have compliance
3 policy guides, we have import alerts and
4 bulletins, we have assignment memos from our
5 centers, we have a regulatory procedures
6 manual, we have a lab procedures manual, we
7 have the pharmacopeia such as USP National
8 Formulary, and we have analytical methods
9 references such as AOACI's official book of
10 methods.

11 Then we have our own quality assurance
12 program, QMS program, that I mentioned earlier.
13 And then investigators, op manuals, fax data
14 manual and others.

15 So essentially, the intended use of
16 the data drives the level of science necessary
17 to determine the credibility of our decision-
18 making on various regulatory issues.

19 And really in a sense, fitness for use
20 is an iteration of customer-provider
21 interaction. The customer who will use the

1 scientific data for some purpose needs to
2 clearly articulate the full scope and the
3 purpose of the science, that that science will
4 serve.

5 The provider of the science, which
6 would be us, is in the role of delivering the
7 goods according to agreed-upon specifications.
8 The fitness for use process is by design and
9 necessity a dialogue and a negotiation. All
10 parties must be clear on their mutual
11 understanding of what is to be delivered and
12 how the deliverable will be used.

13 The relationship continues even after
14 the science is delivered, because essentially
15 responsibility or the credibility of the
16 science remains with the investigators,
17 scientists or compliance officers. They are
18 the ones that are called upon to explain and
19 defend this science whenever we get into
20 situations such as the courtroom.

21 And within many organizations there

1 are procedures that present exist that can
2 become part of our fitness for use process. In
3 FDA, when an investigator collects a sample,
4 that person is to indicate the reason for the
5 collection. For example: Suspected
6 postprocessing contamination with raw
7 materials. And the kind of analysis that
8 should be performed on the product.

9 [Slide]

10 For those situations not covered by a
11 specific compliance program, the investigator's
12 description of the events must focus on the
13 kind of science needed to basically support the
14 desired compliance decision or actions we're
15 going to take. Again, constant ties to the
16 scientific information.

17 And there has to be a culture within
18 the organization that encourages communications
19 between the customer, which would be the
20 investigator or program person at headquarters,
21 our partner in a state or local authority for

1 that matter, and the science provider. And we
2 must also consider the needs of others who may
3 become involved such as our compliance
4 officers, headquarters staff, attorneys, both
5 their attorneys and our attorneys; and anyone
6 else with a vested interest in the process.

7 Successful outcomes in the context of
8 fitness for use of scientific data requires
9 participants to understand not only their roles
10 and responsibilities but also those of others
11 involved in the process.

12 Actually, another way of looking at
13 the fitness for use concept is contractual
14 scope of work.

15 This game plan really entails ensuring
16 that number one, both parties are in agreement
17 on the specifics; and number two, share a
18 vested interest in achieving the intended
19 impacts and outcomes.

20 How would this work in our program
21 areas? We look at various components,

1 activities that ORA is engaged in to effect a
2 seizure of regulated product for the presence
3 of pathogens. And the following example I'm
4 going to give you, we'll be looking at the
5 inspection, investigation sample analyses,
6 compliance assessment, regulatory follow-
7 through, and so forth.

8 [Slide]

9 So let's take a look at a food-borne
10 illness investigation, an epidemiological
11 follow up. I pulled one out of our litany of
12 actions that we've had over the last few years
13 to give you some idea.

14 The scenario is an injury complaint
15 where some people become ill after consuming a
16 salad prepared by a large interstate
17 processor/manufacturer. We do have quite a few
18 of those nowadays; they supply salads to
19 restaurants and what not across the country.
20 Our investigator determined, through
21 epidemiological follow up, that the salad was

1 the likely problem.

2 Subsequent investigation at the
3 producer of the salad demonstrated through both
4 inspectional observation and the collection of
5 samples that the firm was contaminating the
6 finished product with raw ingredients coming
7 in; plus they weren't cleaning up their
8 equipment. So we had a twofold problem going
9 on in the plant.

10 Lab analysis of the raw processed and
11 finished product along with tests, clinical
12 samples from the state epidemiologist found
13 that the same species of Shigella was involved
14 in this particular outbreak.

15 The firm declined to clean up and
16 recall the tainted product. The FDA proceeded
17 to seize the salad after embargo by the
18 involved state. So we had a complementary
19 action going with our State officials.

20 The ORA science stakeholders or
21 customers include the investigators, the lab

1 scientists, compliance officers, center program
2 and compliance staff, the Office of
3 Enforcement, the Office of Chief Counsel,
4 Department of Justice, State representatives
5 and others in this particular process. To
6 accomplish each of their roles, they need
7 scientific information and data upon which they
8 can base their consumer protection decisions
9 and move the action.

10 For example, looking back at the salad
11 investigation, the investigator needs to
12 determine where and how the contamination
13 occurred, as it could have been for many
14 sources, or basically determine if it was
15 something outside the scope of the
16 manufacturer. And then the investigator would
17 need to gather the evidence that would make a
18 compelling case, essentially as to how the
19 contamination occurred and make the ties
20 together.

21 The lab scientists need to determine

1 which pathogens may be implicated based on
2 symptoms, onset times, et cetera, so they can
3 isolate and identify the culprit organisms.

4 So this gives you just a very brief
5 glimpse of ORA. As I mentioned, we're at the
6 early stages. There are a lot of scenarios
7 that we plan to look at here. As I mentioned,
8 this is just in the food arena. We do have to
9 take a look at drugs and devices as well to see
10 where we're doing well and where we're not
11 doing so well. And we are planning to look at
12 successes and failures here, and then balance
13 in with our overall quality management system.

14 So with that, I'll call it quits up
15 here and ask for your feedback. We'd like your
16 ongoing feedback as we proceed along this.

17 DR. LANGER: I think you're going to
18 get some.

19 DR. ANDERS: Dennis, could you tell us
20 how the review committee -- what the
21 composition of the review committee will be and

1 how it will be selected?

2 MR. BAKER: We're at the infancy
3 there; we're just developing the committee.

4 DR. ANDERS: Can you give us any
5 preview of where you're headed?

6 MR. BAKER: Well, the basic review
7 committee, we're going to have both internal
8 and external people. We have to involve both
9 our state counterparts to take a look at our
10 overall processes as well as our internal
11 people.

12 Plus, we'll be looking at our own
13 science advisors in the field. We have a
14 number of science advisors that the are
15 assigned to our regional offices, and they'll
16 be taking a look at it from external review
17 purposes, as part of the committee.

18 DR. ANDERS: I'd also hope you'd give
19 considering to Ed's top ten approach.

20 MR. BAKER: Absolutely.

21 DR. ANDERS: It's an great idea.

1 MR. BAKER: I thought that was a great
2 idea. Certainly will.

3 DR. LANGER: Harold.

4 DR. DAVIS: In both cases this morning
5 that we've heard, you listed some of the people
6 you thought would be impacted by this, or who
7 the stakeholders were, et cetera.

8 But in your example that you gave, I
9 would hope you'd actually talk to the salad
10 maker as a part of the review. You listed
11 several people who might be involved. But I'd
12 like to see what the salad maker thought about
13 how you used science to do what you did.
14 Hopefully it doesn't turn into a gripe session,
15 but I think those people ought to be part of
16 the review.

17 Also in neither case did I hear a
18 timeline in terms of how long this thing was
19 going to go on. Sometimes reviews, they become
20 entities unto themselves, and in either case
21 that I hear, "What are we going to do with the

1 data?" You know, are we going to wind up with
2 a report that's going to go somewhere and never
3 again to raise its ugly head; or are we looking
4 for ten recommendations to come out of this for
5 going forward, et cetera.

6 So I think we have to be careful we
7 don't generate a notebook that nobody will ever
8 read, and the only people who will get anything
9 out of it are those people who were actually
10 involved in the process.

11 So I'd be careful with that.

12 MR. BAKER: Well, thank you. We are
13 cognizant of our propensity to develop reports
14 that are subsequently filed --

15 (Laughter)

16 We've got, as I mentioned, quite a few
17 new players in ORA. And that's really very
18 good, because they're receptive to changes that
19 are necessary to get the job done.

20 We're doing a number of things right
21 now and we'll be proposing to really kick this

1 off after October 1. The reason for that is I
2 just charged them with getting their
3 productivity up and so they're all drilling
4 down into their respective districts to make
5 sure that our people are getting out and doing
6 their inspectional work. And I've got them
7 focused on that for the next few months,
8 because I didn't want to really pull them out
9 to start the full process. We'll continue our
10 own development and are putting together the
11 overall committees, but we'll be in the review
12 after October 1.

13 DR. PICKETT: I'm assuming at the end
14 of the process that there will be a set of
15 recommendations that will be made. And I'm
16 curious whether or not within the agency there
17 is a process to implement changes that might be
18 recommended.

19 MR. BAKER: Actually, there is within
20 ORA in our new quality management system. I
21 keep calling it new; we started it about two

1 years ago, have piloted it in Denver and are
2 now putting it in place in each district.

3 It's resource-intensive from the
4 standpoint that you have to have someone
5 constantly monitoring the quality, taking a
6 look and making sure everybody follows the
7 guidelines and does everything as they should.
8 But definitely this can be incorporated into
9 our quality management system, and then become
10 a component of how we do business.

11 DR. DAVIS: You mentioned there were
12 19 district labs or offices?

13 MR. BAKER: 19 district offices,
14 correct.

15 DR. DAVIS: And 16 or 13 have new--

16 MR. BAKER: 16 have new district
17 managers.

18 DR. DAVIS: Are these internal
19 managers? Are these all people from the
20 outside? I'm trying to get a sense of, "Wow,
21 should we be worried that all these places have

1 new people who are just now having to learn
2 their organizations, et cetera? Is this a good
3 thing, a bad thing, or? Seems like a lot of
4 new people for a group that's about to
5 undertake "how do we do what we do" when the
6 people there may or may not know what they do.

7 (Laughter)

8 MR. BAKER: The 16 people that are
9 currently in place all came from either the
10 field or from the laboratory side of ORA; so
11 we're fortunate, they were a combination of
12 both first line supervisors and middle
13 managers. They're new from the standpoint of,
14 they have got new responsibilities and they're
15 managing a district-wide operation, where in
16 the past they may have been more focused let's
17 say as a director of the investigations branch,
18 focusing strictly on the investigations,
19 responsibilities, and not having a direct
20 responsibility let's say for compliance or
21 laboratory functions.

1 So from that standpoint some of them
2 are in a learning mode to better understand
3 compliance and laboratory operations and how
4 they're done. But they do know the
5 organization.

6 DR. ROSENBERG: One of the things that
7 struck me as you were going through that is
8 that given the breadth, the number of levels,
9 the different types of components that you deal
10 with -- is there a concern that if you try to
11 review it all, you'll end up doing a relatively
12 superficial look at too many things, too many
13 components and really not get to where you want
14 to get at the end of this.

15 Have you considered as to whether you
16 should do it all or whether you should pick
17 components of it? As Ed mentioned, reviews
18 aren't one-time affairs; they can be done such
19 that you can walk through this and pick various
20 components of what you're doing. It just seems
21 to me that the scope you have to cover is just