U.S. Food and Drug Administration

Science Board

Meeting

November 17, 2000

9:00 a.m.

FDA Building

CDER Conference Room-1066

5630 Fishers Lane

Rockville, Maryland

Members of the Board in attendance:

Robert S. Langer, Sc.D., Chair

~~Charles A. Sanders, M.D.~~ did not attend

Rita Colwell, Ph.D., S.Sc. (Hon.)

Marion Nestle, Ph.D., M.P.H.

Owen Fennema, Ph.D.

Martin Rosenberg, Ph.D.

Edward M. Scolnick, M.D.

Robert M. Nerem, Ph.D.

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

Marion W. Anders, D.V.M., Ph.D.

Michael P. Doyle, Ph.D.

Invited Guest:

Jane E. Henney, M.D., Commissioner

FDA participants:

Elizabeth D. Jacobson, Ph.D., Senior Advisor for Science, FDA

Bernard A. Schwetz, D.V.M., Ph.D., Deputy Commissioner of FDA (Acting)

Susan M. Bond, M.S.

~~Susan K. Meadows~~, M.S., Executive Secretary, FDA Science Board

Agenda

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P R O C E E D I N G S

DR. LANGER: I'd like to call the meeting to order. My name is Bob Langer, and I'm Chair of the Science Board, and I thought maybe as a first step we'll go around the table and ask everyone to introduce themselves, just briefly. So we'll start with Harold.

DR. DAVIS: Good morning. I'm Harold Davis from Amgen, a biotech company located in Thousand Oaks, California.

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

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

DR. SCOLNICK: Ed Scolnick, I'm President of Research at Merck.

DR. ROSENBERG: I'm Marty Rosenberg, I head infectious disease research at SmithKline Beecham.

DR. FENNEMA: Owen Fennema, Emeritus Professor of Food Chemistry, University of Wisconsin-Madison.

DR. ANDERS: Dreg Anders, Professor and Chair, Department of Pharmacology and Physiology, University of Rochester.

DR. NEREM: Bob Nerem, Professor and Director of the Institute for Bioengineering and Bioscience at Georgia Institute of Technology.

DR. COLWELL: Rita Colwell, Director of the National Science Foundation and representing interagency cooperation.

DR. HENNEY: Jane Henney, Commissioner of FDA.

DR. LANGER: Bob Langer, Professor of Chemical and Biomedical Engineering at M.I.T.

DR. JACOBSON: Liz Jacobson, Acting Senior Adviser for Science at FDA.

DR. SCHWETZ: Bern Schwetz, Acting Deputy Commissioner of the FDA.

MS. BOND: Susan Bond, Office of Science, FDA, and Executive Secretary of the

Board.

MS. FOREMAN: Christy Foreman, Office of Science, Executive Secretary for the Board.

DR. FEIGAL: David Feigal, Director, Center for Devices and Radiological Health.

DR. BUCHANAN: I am not Joe Levitt. I'm Bob Buchanan, Senior Science Advisor for the Center for Food Safety and Applied Nutrition.

DR. ZOON: Kathy Zoon, I'm the Director of the Center for Biologics.

DR. SUNDLOF: Steve Sundlof, I'm the Director of the Center for Veterinary Medicine.

DR. BAKER: I'm Dennis Baker, the Associate Commissioner for Regulatory Affairs.

DR. CASCIANO: Dan Casciano, Director of the National Center for Toxicological Research.

DR. LANGER: Thank you very much.

We're going to have Dr. Henney make a few comments, but before doing so, I just wanted Christie Foreman to make a few housekeeping announcements.

MS. FOREMAN: There are telephones located by the guard, in case anybody needs to use the telephones. The restrooms are located right outside the door.

We are transcribing, so if you could please talk into the microphone -- and hopefully we won't have feedback like that. To turn them on, you can touch them, and if they don't seem to be working, you can actually pick them up and bring them to you.

We do have two scheduled breaks today; one at 10:45 and one at 3:00. We will break for lunch from 12 to 1 and we do have our NCTR group on the Polycom, so they may be joining us shortly.

DR. LANGER: Thank you.

Jane?

Introductory Remarks

DR. HENNEY: Good morning and welcome. I'm just delighted to be here. As you all know, I was unable to come last year so I'm more than thrilled to be well enough to be here this year for this meeting.

I would like to underscore how much we need you. We need to benefit from your advice because it is I think absolutely critical in the pace that's going on in science and technology. This agency needs your help now more than ever.

I think there are three things that I would bring to your consideration in terms of our need for strong science at the FDA.

First and foremost, consumers have had confidence in this agency because of the scientific strength of our decision-making.

The recent Pew study done this spring and the results released, it was done of all of the regulatory agencies of government. An overwhelming percentage, 75 to 85 percent of those surveys said they trusted FDA to make the right decision, and 74 to 87 percent believed FDA used good science in their decision-making.

So I think a linkage between trust and using science, objective members to ground our decision and policy making is really underscored by that.

This wasn't exactly a just-man-on-the-street kind of interview situation. Either it was four groups that were surveyed, clearly medical and health professionals, members of the patient advocacy groups, consumers, and then regulatory officers of much of the regulated industry who interact with us.

And the results across the board were quite consistent.

So in terms of keeping that important element of consumer confidence, consumer trust in those products that we do regulate, it's absolutely essential that we have the kind of staff on board and the capabilities to reach out to gather the kind of science we need to make good decisions.

I think the other thing that I would raise is something that you know and know well, the increasing investment that this country is making in research and development.

And clearly the end result of all of that investment, hopefully, will be new products coming to market, and we are really

the interface with that review process.

So having the scientific capability and the regulatory presence to make those decisions means that science at this agency must be strong.

The third thing that has really upticked, if you will, in the last decade is something we also all know; and that is increasingly aggressive trade police as a national policy, and to really affect in a reasonable way new treaties that are taking place with other countries, with other governments, we need to have the scientific presence and the scientific skill to make sure that the standards set in those negotiations are a high standard.

We need to have a presence when disputes arise to make sure that we can be scientifically present and at the table making our case in terms of any disputes that do arise;

And we need an ongoing presence of those scientific issues that are coming about

through all of really increased impact of globalization.

I would say that we have an over abundance of scientific issues that face the agency at any one time. I think just within the last month I would tell you sort of what has been sort of our minds.

Some of these have been on our minds but they have reached a different level of urgency or a different level of compelling need, clearly antibiotic resistance.

Things like the information that is rolling out of the human genome project, the genomics and the proteomics areas, all of the issues around bioengineered foods.

Clearly, the issues around transgenic fish, not only as a food product but its impact on the environment as well.

Decisions that we're making about products that come to market, products that must be removed from the market.

I would also bring to your attention some scientific policy matters, if you will,

that we're also at a point of real discussion this past month; things that have been worked on for some time, but our participation in the Internet -- ICH or the chromotization efforts.

This has been a decade-long effort between the regulatory bodies and the industries of the U.S., the EU and Japan.

And just last week, I think, we had a session where we have come to the point of harmonizing between all of these countries and regulatory bodies on many elements, what is to be provided to the regulatory bodies by industry, resulting in a common technical document, a common dictionary to be used, reporting different events, and reporting on products that are being used.

This was no small undertaking, and people had to work very intensely on this effort. There's still much work to be done. But, again, we have to from this Agency's standpoint, have strong science to participate and hold our own in those kind of discussions.

I would just leave my welcoming

comments with that to give you a flavor of some of the kinds of things that we deal with.

I also wanted to bring to your attention some things that are going on in my own office in terms of either personnel or organization.

Clearly, after you met last year, I asked Dr. Schwetz if he would give up at least for a time one of the hats that he was wearing and become the full-time acting deputy commissioner, and he said he would.

But it also gave us an opportunity to ask Dr. Elizabeth Jacobson to take on the task of acting as the senior science advisor for science in my office.

For those of you don't know Liz, she's an extraordinary person and scientist. She was early winner of the Fleming Award, as I recall. She's worked for many years in the research and the science policy area, in the Center and Devices, and has been really a wonderful addition to our staff.

We have created a new office in the

Office of the Commissioner, also the Office for Clinical Science. We now have a person, Dr. David Lepai, who had been working in the Center of Drugs, detailed to that office while we're recruiting a person to head up that responsibility, largely looking at many issues in clinical science across the agency but particularly on those matters that deal with human subjects protection.

We also have a new function in the Office of the Commissioner, and that person is coordinating all of the different Centers and field efforts in the whole effort of bioterrorism preparedness.

Ellen Morrison from the field came in and pulled together a team in terms of making recommendations on how FDA should proceed in these initiatives. And Dr. Gary Tchikami is now on detail to help develop a strategic plan in that area.

Both of these positions are being advertised, both the ones for clinical science as well as the one for bioterrorism. As you

might know of candidates who might fill these positions on a full-time basis, we would welcome your input on that.

We also have, I think, another thing to recognize on the staff. I would like to recognize the fact that Bern just recently received a very high honor and award from the Academy of Toxicology and just was out there and giving a major address.

And our Center on Drugs has just been told in terms of their training programs, they will be the recipient of one of the Deming awards. So we're very proud of those accomplishments.

In terms of other recruitments, again, asking you to put on your thinking cap and networking cap in the National Center for Toxicological Research, Dan is searching for his deputy director for research.

And over in CFSAN we are looking for a person to take on the role of food safety. Susan Alpert, who had been in that position, just left the Agency a month or so ago.

So those are another two key spots I think where we need people with strong scientific and research credentials in those particular positions.

I will close my remarks with that.

I also know that you have a very busy day planned for you by the Office of Science, and so I will turn it back over to you, Mr. Chairman.

DR. LANGER: Thank you very much.

Bern, I'll turn it to you to make some introductory comments.

Introductory Comments

DR. SCHWETZ: We wanted to use this morning to talk about emerging science issues that the Agency needs to be prepared for as we look in these next few years, and specifically from the standpoint that new science drivers, new products, new products drive, new questions, new issues, and the issues have significant implications for the resources that we need, the types of expertise we need to deal with those issues, the facilities that we need

to do laboratory work and other work that's related to these issues.

So over the past year we've been pulling together information from throughout the Agency, from the Centers, from the field group that relates to what we collectively think are the emerging issues and have begun to look at them from the standpoint of priorities and the implications for the types of people we need to have in the future to deal with the issues that these new products will represent.

We feel that the right of change of new science, new products, new technology coming to us is going to be faster than it has before, and we don't want to be in the spot of watching what happened today to try to decide what kinds of expertise we need.

So we're trying to anticipate how do we match up the recruitment and the molding of the Agency scientist profile so that we're staying up with what we anticipate to be the emerging science needs over these next years.

So Liz Jacobson and the Center

Directors and Dennis Baker are going to be talking about the bigger picture, in the case of Liz, and the people from the Centers talking about some specific examples of emerging issues from within their Centers.

We want to talk with you about these and your reaction to these issues, your thoughts about the relative priority of them, the implications that these issues have for the expertise profile that we need to have in the future and how we'll get at those people to recruit them.

From within this bigger picture and the examples that will be laid out, we also want you to think about specific pieces of this picture and the examples that you would like to have brought back to the board for more in-depth discussion in the future, because there are some of these that are going to be much more difficult to deal with just because of their novel nature than some of the others.

And we would really like to pick your brain on how to find the experts to help in

this, what do you think is the real priority of some of these things, or do you disagree with our opinion of the likelihood that these will come to be issues?

So that's the kind of presentation and discussion we'd like to have this morning. So I won't say any more except to turn it over to Liz.

Challenges and Overview of Issues

DR. JACOBSON: Trying to get a handle on this topic really wasn't very easy. We have certainly a plethora of challenges, as Jane said.

The plan for the morning is to talk about the challenges that FDA faces in terms of emerging issues or in some cases in terms of issues that are already here.

(Slide.)

The intention was to have a general discussion, and then in subsequent meetings of the Science Board to discuss in-depth perhaps some specific issues that you particularly are interested in.

The point is that when it comes to the challenges that we face, we'd like to be able to ride the wave of innovation in science and technology like the school surfer that you see and not get overturned like the Andrea Gale.

Next one. (Slide.)

I'm going to discuss some of the challenges and do an overview of emerging issues, and then each of the Center Directors and Dennis Baker will spend a couple of minutes on specific issues that they're contending with, and then we'll have some discussion, both on the issues, per se, how do they strike you and what do you want to talk about more in-depth next time.

And we'll also talk about the strategies that FDA should be using to meet those issues.

Next one. (Slide.)

So what is the challenge? Well, to try to sum it up in one slide, we really feel that our ability to make quality and timely decisions is strained, and the reason is

because science and technology are booming, which is a good thing, but it's not easy to keep up with that.

Government and industry are making very big front-end investments in research and development, but we don't really have any indexing of that research and development investment to FDA to match what's going on, and not surprisingly, the number of submissions is increasing, and the kinds of submissions that we get are also becoming more complex.

(Slide.)

This slide just illustrates part of the investments. It doesn't even give all of the government investments in R&D. You can see both industry and NIH, the big bars in the back, and then FDA investments are the small bars, the relative investment and regulatory science is much smaller.

Next one. (Slide.)

PhRMA found that, not surprisingly, this wonder investment in research and development is really paying off in

biotechnology products, for example.

PhRMA did a survey this year, and they found some 369 products in the pipeline in a survey that they did. Now you can argue the numbers in terms of well, is it really 369; what is it?

But I think you can't argue the trend that increases in research lead to product payoffs.

(Slide.)

In spite of the sort of divergence and support that I talked about, expectations of FDA by the public are really very high. We have a long history of public health protection at FDA, and ~~Americans~~ have really come to depend on it.

They ~~want the products that are resulting from the science and technology revolution.~~

~~They expect to get those products as soon as they're reasonably available, and at the same time they really trust that the system is going to alert them to any problems,~~ and

they recognize that FDA plays a part on that alert mechanism.

Next slide. (Slide.)

This slide shows a different survey, actually, from the one that Dr. Henney mentioned. This is a survey done by Research America. And it showed that 70 percent of the general public surveyed knew who FDA was and what we did. In general terms, but they were familiar.

Compared to some 4 percent of people who knew what NIH was and what they did. So we really have a lot of public recognition, and we need to continue the best safety net possible for the public.

(Slide.)

I guess the point I'm trying to make here is that our output may look a lot different from that of NIH or CDC or NSF or other scientific agencies because we're regulators. But our impact on public health is every bit as dependent on our being masters of the current science as theirs is.

And most importantly, we have the potential as the gatekeepers of new technology to have a very powerful impact on the flow of that technology to people who need it. We're very aware of that possibility.

It doesn't matter whether you're talking about drugs and devices or genetically modified plants and animals or gene therapies, we still have a very important role to play.

Dr. Henney has said on several occasions that we stand in judgment, really, of the best efforts that industry and academia are putting forth so it's very important that we also have very high quality.

(Slide.)

In trying to do an overview of emerging issues, we decided to group them in a number of categories. You can see them here and also there's a copy of my handouts in your package.

A lot of these categories contain a mix of issues that are emerging and those that are here now, and also it really does seem to

be a truism for us at FDA that many issues never go away and old ones come back, or they recycle and they come back in a slightly different form.

Next overhead. (Slide.)

Under New Science and Technologies, we have things like genomics and proteomics.

Pharmaceutical houses are already anticipating huge changes in how drugs are developed, and today's highly inefficient approaches are envisioned to be replaced by elegant bioinformatics driven drug discovery.

In terms of tissue engineer products, we're already seeing hybrid bioengineered products are biology is meeting engineering and where new biomaterials are being used in very exciting ways.

This poses interesting scientific questions and also interesting regulatory questions in terms of which center has jurisdiction.

In robotics and nanotechnology, Bill Joy of Sun Micro Systems listed genetics,

robotics, and nanotechnology as the three most powerful 21st century technologies.

He worries that these three carry hidden risks of huge dimensions because they're self-replicating and they'll be able to be used by many individuals and small groups.

We don't claim to be as envisionary as that or to be worried about that aspect of things, but robotic applications and medicine are here today and we need to be able to assure their safe and effective use.

In July, we approved a robotics surgical device, for example, that allows surgeons to perform surgery while seated at a computer console that's remote from the patient.

And the surgeons say that although the computer controls the instruments, it feels as though their fingers are grasping the tip.

So it's fun to imagine doing surgery on a patient in a remote setting, somebody in Antarctica being operating on by their surgeon at Mass General, but first we really need to

raise the complicated questions that are raised by robotics and engineering, software safety, and human factors design, and a number of other disciplines.

Nanotechnology is also no longer science fiction. In April NASA and NCI announced a Memo of Understanding to develop nano explorers, their term, for the human body in the form of injectable nano robots or nano bots that will roam the body to detect, diagnose and treat disease.

And that kind of leads into the next category, biosensors. These little nano bots would be biosensors, and probably drug use delivery systems as well.

But there are other applications of biosensors that we're already seeing.

Our scientists in-house developed a chemical sensor to identify deteriorating seafood in the package.

We are also evaluating a hand-held advance nucleic acid analyzer that was developed by Lawrence Livermore to identify

infectious agents, and we really see this as a type of instrumentation that would have incredibly wonderful applicability to the needs we have in our field operations.

Transgenics, of course, is in the news a lot, in all kinds of applications, including gene therapies and starlink (ph) corn.

I think in an application you may be less familiar with, Atlantic salmon can be genetically modified with growth hormone, and they reach their full size and therefore their market ability point many days before unmodified salmon, so there's lots of applications of this technology, and our job is to assure that there aren't any adverse health consequences to these kinds of modifications.

The next one. (Slide.)

The next general area is information management. I've already mentioned bioinformatics as it relates to the products of genomics and proteomics, but we also have many applications in-house and some medical devices already approved, as a matter of fact, that

employ artificial intelligence so this is obviously quite a step up from the computer-driven instrumentation that we think about.

We within FDA have just begun a strategic planning effort in the area of knowledge management. Like the rest of the world, we own a tremendous amount of information, and we're getting volumes more pouring in every day, and we basically need to figure out how to know what we know and how to make that corporate knowledge base available and accessible to our staff who have knowledge needs.

And, of course, there's a lot of interest in using computational approaches for predicting biological activity and toxicological properties of chemicals.

In one sense, the next category is called public health questions, and officers in one way all of these things are public health questions.

But here I'm really referring to specific problems that may be new or recurrent,

and I'll just mention three of them.

One that's been around for a while is antimicrobial resistance. It cuts across all of our centers. Each one plays a role in some aspect of dealing with resistance bugs, from approving the drugs that go into animal feeds and evaluating devices that have growth-inhibiting coatings.

We also have a role to play in antiterrorism efforts. People don't usually think of us in terms of anti-bioterrorism, for example, but many of the drugs that have been proposed for treating bioterrorism agents haven't been evaluated or labeled for those indications, so there's really quite a role that we need to play there.

Next one. (Slide.)

The next category: Better tools and methods, also a rather broad category. We need to keep up with quantitative risk assessment and modelling. We play a critical role in the science of clinical trial design and analysis.

We need better predictive tests for

things like alternatives to animal testing and better biomarkers.

How, for example, can we better predict hepatotoxicity.

And we also need better methods, more rapid, more field rugged.

Earlier I mentioned the hand-held nucleic acid analyzer.

We also need better tests for other things, like food-borne and waterborne parasites or viruses.

We don't have regulatory methods for natural toxins and seafood and algae that are found in dietary supplements. The methodology for detecting allergens, such as peanut allergens, in unlabeled products is not well established.

We need rapid methods for microbiology that are validated, that are able to work in various matrices.

And we need to look at food processing steps to see if we can intervene and reduce the incidence of food-borne illness.

I think the Center directors each will have a long list of methods that they need that are particular to their Center.

The point I'm trying to make here is that the public thinks we can test for everything, and we can't.

Next one. (Slide.)

Well, this brings us to the people related part of our issues, and the first one I wanted to touch on was the flexibility of our workforce.

We have a lot of issues here. You talked about some of them at your last meeting, training and retraining, recruiting high caliber people.

You're going to hear an update this afternoon about the recruitment effort that CFSAN has going on, our Center for Food Safety and Applied Nutrition.

You'll get some feedback as to how that recruitment effort is going.

Retention of the staff that we have is also important. The Agency-wide attrition rate

from '95 to '99 has actually gone down slightly. Our overall attrition rate has gone from 7.2 in '95 to about 5.8 in '99.

If you look at scientific categories, specifically, the attrition rate for 5 of 9 scientific categories has gone up very slightly. They're all under 9 percent, but the trend in several of those -- biologists, pharmacologists, math stats, computer scientists, and microbiologists -- have gone up a little.

Interestingly enough, the rates for chemists and engineers, the attrition rate has gone down slightly. So this is an area we're not quite sure what to do with those numbers, but obviously we really need to pay careful attention there.

We also need to look at what kind of alternatives we have to permanent hiring.

Except for our user-fee programs, we've been continually losing people or not replacing staff when they leave so that we'll have money to put into our programs.

So if we can't do hires, what kind of other alternatives do we have, and that's one of the topics that we want to get into some further discussion with you.

Next one. (Slide.)

The other human issue here that I wanted to talk about is patient rights and consumer needs. The first bullet there, human subjects protection, has been in the news a lot lately. That's something that we are, as Dr. Henney mentioned, put Dr. Dave Lapei in place to pull together our efforts in that area.

But consumers also want freedom of choice, and they want to exercise their right to know. This place is a very big responsibility on us to be good communicators. So not only to do good risk management, which is clearly important, but also to do good risk communication of that risk management.

If we don't communicate clearly to the public, if we aren't transparent and open to questions, then we're ultimately going to fail because they won't believe what we say.

We also need to be sure that we understand human behavior, because it really plays a role in everything, from what information you put on a label and how you display it to how you arrange the knobs on anesthesia equipment.

Next one. (Slide.)

So we have to plan for a lot.

We have to plan for a rapidly-changing technology, for a tremendous volume of information, for rapid response to public health questions, for a flexible workforce, and for patient and consumer needs.

Next slide. (Slide.)

We'd like to discuss two aspects of this this morning. First, we'll have the Center directors go around and talk to you more in detail about some of the issues that we just went over.

And then we'd like to get your reaction to the issues and to talk a little bit about which of them you'd like to do more in-depth. I know that Dr. Nerem has already asked

for a future discussion at some date on tissue-engineered products.

And the second question that we wanted to talk about were strategies that we need to employ to be able to address these issues.

Next one. (Slide.)

How can we attract the necessary expertise? And Dr. Schwetz mentioned this in his remarks as well.

I've just listed some possibilities here that we can come back to later on things that -- everything from the current paradigm, hire somebody if you need this particular expertise, to sort of -- that's a business as usual approach -- to getting very creative with collaborations and leveraging type initiatives.

Next one. (Slide.)

Some of the additional questions that we wanted to wrestle with a little bit today are what types of expertise do you think it's going to be particularly hard for us to get and how can we successfully compete for these people?

How do we stay flexible in terms of being able to meet new types of scientific questions as they come along;

And how do we keep our infrastructure developed so that we can put these people to work in the most appropriate way?

Last slide. (Slide.)

I think one thing that is clear, and I've just got a couple of quotes here on the importance of science, is that we can't do this in a vacuum. We have to work with our stakeholders in new ways if we want to be successful in staying scientifically strong, and that's the reason we've sort of orchestrated the session here today is to have some really good discussion on some of these questions.

I think that's the end of my remarks.

I don't know, Bob, if you want to go right into discussions with the Center directors?

DR. LANGER: Yes. I was going to see if there were any questions right now.

Basically what we thought we'd do is have Liz give the talk as she did, then have the Center directors go over some of their specific issues relative to their Centers. And then we have from 11:00 to 12:00 reserved for more general discussion.

But there may be some more specific questions now or comments, and if there are it would be great to hear them.

DR. ANDERS: I have one specific addition to your list. We have genomics and proteomics. There's a new area called metabanomics, which is just starting to emerge. Now metabanomics is the multi-parametric analysis of the metabolic products of the proteol.

And coupled with high field enimaranalysis and bioamphormetic strategies, you can rather remarkable things in analyzing biofluids. The big pharmaceutical corporations, I believe, have formed the metabanomics consortium. They've recognize the advantage of it.

I think it plays into a lot of things that the Agency does and we might want to hear about that from some experts in the field at some future date.

DR. JACOBSON: Sounds good.

DR. LANGER: Bob, do you want to comment?

DR. NEREM: Yes. Maybe when the Center directors make their comments they could help someone like me understand how research fits into a Center and the interface between research that might be part of the Center and the regulatory activity, because it seems to me that that bridge between science and regulation is what we have to try to understand if we're to be of help to you.

DR. JACOBSON: That sounds good.

I didn't try to dissect that out specifically because we were trying to focus this on issues and, really, research plays a piece in each of those issues, even when you get to the human --

DR. NEREM: It may be future

discussion, but I think your research budget is something maybe on the order of $150 million a year. I have no idea how that translates into how it gets done in the organization.

DR. JACOBSON: Okay. Good.

DR. LANGER: Other?

Yes, Rita.

DR. COLWELL: I could probably just amplify in the more general discussion, but I'm fascinated by the fact that the initiative from the National Science Foundation are, in fact, basic research, nanotechnolgy, information technology, mathematics initiative to deal with improving quantitative risk assessment in modelling, prediction modelling, as well as education and training, which is of course one of the topics you've raised.

And we're planning a major initiative in FY 2003 of the social behavioral sciences which the topics -- the subtopics that you list of human behavior, labeling, and even where you put the knobs on the anesthesia machine, it seems to me that there's some very nice

parallel directions for the two agencies and that we ought to find some ways to collaborate and leverage for you the basic research that we do that can be put into practice in a very quick way here at the FDA.

So this is something you might want to cover later in the discussion.

DR. JACOBSON: Sounds great. I mean, that is the kind of synergy that we were hoping would come out of this kind of a discussion.

DR. HENNEY: Liz, you might mention some of the things that we do with other federal agencies like NIH, where we have the MOUs with the Dental Institute and that kind of thing.

DR. JACOBSON: Yes. Actually, I'll mention a couple of them.

Dr. Colwell, we've had several interactions with members of your staff in terms of doing some forecasting of what the future technologies are going to be looking like in 5 to 10 years. That's been a very interesting exercise, and it's resulted in

several workshops.

We also have a Memorandum of Understanding with the National Institute for Dental and Craniofacial Research where they asked us to come and talk to their grantees so that their grantees get an idea of what are the regulatory questions that they're going to be facing when they bring their ultimate research idea that's turned into a product to FDA for review.

And so we get a wonderful heads up on what the early developments are in that particular area of science. And they get, the grantees get, a heads up in terms of what kinds of questions they're going to be expected to answer so they can design their experiments in a way that will lead to less problems at the end and swifter movement of those ideas from idea to product to consumer or to patient.

DR. LANGER: Other questions or comments before we go on?

(No response.)

DR. LANGER: Do you want to turn it

over?

DR. JACOBSON: Yes. Center directors, do you have any preference or should we start at one end and go down or? Start at the other end.

(Laughter)

DR. JACOBSON: Janet, for reasons I know you'll understand, I'm going to do what David says.

(Laughter)

Center for Drug Evaluation and Research

DR. WOODCOCK: I'm Janet Woodcock. I'm the head of the Center for Drugs at FDA.

Can everybody in the room hear me? No.

Can the people hear me now? In the back, can you hear me? Okay, good. I'll try to make this audible.

I was asked just to cover a couple of our science priorities. We have a very long list at Center for Drugs, and so I can by no means discuss all of them.

Liz has covered a number, the range of

issues that we face.

First, we were asked to comment on the research effort and how that fits in to our regulatory programs.

Center for Drugs is really not funded in a way that we can conduct a robust research program, period. We have tremendous needs, both in the analytical area, drug analysis, in the toxicology and biomarkers area.

I would like to have a program and a clinical trial design and analysis because that is a scientific discipline where there are very few foci in the academic realm of how to do that, and yet it is something that we are called to judge on and contribute to every day as far as the design of clinical trials and analysis of clinical trials for registration or pre-enrolled pharmaceuticals.

In addition, we need more research on things like behavioral science. We're constantly asked, you know, do doctors follow the labels, what is the effect of direct consumer advertising on consumer behavior.

We do not have any research dollars that can be put against those.

And, in addition, our whole drug safety area, we have tremendous research needs. There's a large amount of data out there in the world about the impact of the outcomes of drugs, the use of drugs from link databases that are held by managed care and payers and other sources, and we don't have funding to link to those sources.

So in general we don't have a robust research program to discuss because we lack funding to do that.

As far as our priorities, I would say our No. 1 priority is a somewhat global one, and that relates to during safety.

I think the last four decades in the realm of pharmaceuticals has been devoted to determining whether drugs work or not, and there's been a long effort in clinical trial design and statistics and so forth, but we all have that down pretty well.

I think it is rare to nonexistent

where FDA would approve a drug, and people say the drug actually doesn't work if you think about that.

And we've figured out -- and that wasn't the way 40 years ago, 30 years ago. There was often substantial doubt about whether drugs that were on the market worked or not, and that time is over.

But the safety of drugs and predicting how the toxicity and how the drugs are going to behave once they're used in the market is something I think is going to be the endeavor of the next decade or so for us.

And that has a lot of dimensions. We need to be able to predict the adverse event profile, and that has to do with the toxicology, with clinical trial design, but also understanding how products are going to be used out in the marketplace, and something of a behavioral science aspect that we have paid not enough attention to over the years.

And also ascertaining signals and analyzing those signals. And let me go into

that a little bit more.

In prediction, everyone agrees so this is no big news, that we need better, more predictive, preclinical models and more predictive biomarkers for toxicity, and the recent experience over the past save years, say in liver toxicity, after a drug is marketed, has shown us that we still cannot predict accurately -- and we're still going through this with drugs that are before us now -- we can't predict accurately which drugs are going to result in fatal liver failure once they're on the market.

And this is a science issue. These drugs have all gone through animal testing and they've gone through human testing, and we still cannot say which ones are going to have the rare, fatal, hepatic necrosis associated with them.

We're getting better, but we aren't there yet.

And there are other types of toxicity we're still in the dark about. The QT

prolongation for the electrocardiogram and what that's going to be mean. There are a lot of drugs that cause this. What is the actual effect? What is the actual outcome out in the real world?

So that's preclinical. I know people are going to talk a lot here about genomics, but understanding genomic diversity and its effect on toxicity and on drug-drug interactions is an extremely important part of predicting toxicity because toxicity may be a direct result of genetic diversity, of course.

And for the FDA it isn't just a matter of having scientific understanding of this. It's a matter of trying to figure out how can we make sure that the people who are going to use these drugs out in the real world have enough understanding of this that they can use the drug safely?

In my mind, it's all well and good to talk about genomics and so forth, but if you can't get a real world understanding of the

clinical community and alter their behavior to take into account the scientific knowledge it's generated, you're still going to have the same safety problems.

So the challenge of identifying the genetic alterations or phenotypic alterations is just the start, at least from a regulatory point of view.

Clinical testing methods for prediction. We look at the animal and the clinical testing as a sort of continuum. It has the same degree of challenges as far as trying to determine from the clinical results and predict the toxicity out in the real world. We still are not there yet.

As i said, capturing and disseminating this knowledge in a way that just isn't out there but is actually effective in making sure that behavior is modified appropriately based on the knowledge.

Right now, in clinical medicine, we know much more than is effectively translated into clinical practice, and the lack of

transfer of that knowledge impacts very severely as the recent IOM report on medical errors brought out. It impacts very severely on safety in a negative way.

Now, as far as ascertainment and risk assessment, in the post-marketing area, we have a tremendous need for better ways to not only detect signals of toxicity, which is what we do now with our spontaneous reporting system, we get hints of toxicity that's occurring out in the real world.

And we get about 250,000 reports yearly of adverse reactions to drugs that are spontaneously submitted to either the manufacturers or us. But then we have to have better ways of analyzing these data, and we can't just look at the spontaneous reports.

They're inadequate. They lack a denominator.

They don't tell us about incidents or causality, for that matter, and we're having tremendous debates about this in very public quorums.

The withdrawal of phenylpropanolamine, potential withdrawal from the market, that was recently in all of the papers, it's an over-the-counter medication that's been on the market for decades, but we feel is associated with a higher probability of hemorrhagic stroke in young women who take it.

It took us 15 years, at least, to develop an appreciation of the causal link well enough to make this recommendation to the public, and we've got to do better than that in the future.

My second point, and I don't want to take too much time, another issue that I think is really a key for Center for Drugs, and we've put a tremendous amount of effort into this, and it really is becoming a scientific discipline, is knowledge management.

We are basically, in the Center for Drugs, information or knowledge workers. We get tremendous volumes of knowledge and information and we process and analyze that information, and we have information outputs,

and we must develop better medical informatics.

And I have a list here of the types of things we're working on. We are putting a lot of effort and work into this but we need to bring it to a much higher level to be effective in the future especially as all of this informatic information is going to start to pour into us from all the scientific efforts that are going on.

So those I see are two of our highest priority science issues that we'll be dealing with.

National Center for Toxicological Research

DR. CASCIANO: I'm going to go to the podium.

We at the NCTR do not have a direct regulatory mandate, but we do provide regulatory scientific background for the agency.

Could I have the next slide, please.

(Slide.)

The issue that I decided to discuss is the issue of better predictive tests, and we at

the NCTR feel that our mission is to develop, modify, characterize and validate better predictive toxicological tests.

We are working in these various specific areas, and I'm going to tell you a little bit about the DNA and protein-based technologies.

Greg, Drag we just hired a new division director of chemistry who's very interested in metabanomics. We're in the process of developing programs in that specific area.

I'll tell you a little bit more about that in my subsequent slides.

We've developed transgenics, both transgenic mutational-based systems as well as carcinogenesis-based system that we're in the process of validating.

And, of course, we're interested in understanding the toxicology response that occurs in the human and not in our rodent surrogates, and so we are constantly looking for rodent homologues for biomarkers.

An alternative, the animals, we have a

program in developing human tissues, primary human cell cultures to help us understand and predict the human response and, of course, computational science underpins everything that we do.

Next slide, please. (Slide.)

And this is a slide that you've seen many times, and I'm going to tell you two projects we have undergoing in the DNA area. The proteonomic area we're just beginning to develop.

The two projects that we have ongoing are placed on this slide.

Human genotyping and use of gene expression profiles to predict outcome.

Next slide, please. (Slide.)

The gene expression profiling direction is based on utilizing primary rat cells from a variety of different organizations and exposing rat cells to known carcinogens or mutagens, and evaluating gene expression profiles.

And then utilizing the same technology

to investigate exposure of the particular organ to which that toxicant is directed;

And utilize then primary cells, human cells in culture, and be able to predict human responses.

So we have a relatively large program developed in that specific area.

Next. (Slide.)

Dr. Fred Kalibur at the NCTR is developing a risk chip -- he calls it a risk chip. It's a single nucleotype polymorphism chip that the polymorphs are constituted in xenobiotic metabolism enzymes and the p450s and in the Phase 2, two enzymes, and he's also developing DNA repair polymorphs on this chip.

He is collaborating with and leveraging with genometrics in Houston, and they're just validated a mini-chip to indicate that the process by which they are developed has potential merit.

Next slide, please. (Slide.)

Many of us in the various toxicological disciplines have been doing

proteonomics for years, we just didn't call it proteonomics. Now we're beginning to gel that apparatus to apply it to our surrogate systems as well as the humans, and protocols are beginning to be developed in these specific areas, and we're going to be moving in this direction at a high level in the future.

Next slide, please. (Slide.)

What are our problems? The problems we've attempted to identify within the Agency is whether or not we should develop our own chips, or should we be utilizing commercially-developed chips?

And, of course, we have the problems that everyone has, is how do we staff the bioinformatic requirement is associated with all of the new technology that I just discussed, and how do we supplement our staffs in that particular area, is a very difficult problem, especially if you're located in the middle of Arkansas.

So any help you can give us, people who are looking for the natural environment,

who are hunters or fishermen, we would be very appreciative.

I think this is the last slide.

(Slide.)

We are attempting to utilize creative equipment other than traditional recruitment procedures, and if you have any suggestions or ideas on how we can enhance that, I'd be very interested in hearing them.

Of course, leveraging and collaboration, this was mentioned by Liz in her discussion, and we have also the ability to purchase academicians for short periods of time.

This is through a methodology of interpersonal act, and we can buy academicians who are interested in spending more than just a single year as a sabbatical with us, and that's one mechanism that we are using to supplement our deficit in the bioinformatics area.

So if anyone has any questions, I'd be pleased to respond.

DR. LANGER: Questions or comments at

this point?

(No response.)

DR. LANGER: Okay.

Office of Regulatory Affairs

MR. BAKER: The Office of Regulatory Affairs, of course, is the field organization for the agency, and many of the issues that Liz brought up this morning are direct issues for our office.

We are basically the sensory system for FDA, with our employees moving across the nation and across the world.

Our employees have to have the ability to cover all areas for the Centers. They've got to be steeped in science to be able to understand and identify new issues and determine if concerns warrant the attention of the agency.

They also have to understand how decisions of other government agencies directly impact what we do.

And I guess the last thing they have to do is they have to educate, and so we've got

a broad-based group of people to do these things.

We operate out of five regions, 20 districts, and 13 laboratories doing the regulatory work.

And we've had, unlike some areas of the agency, we have had a tremendous turnover in staff. In the last couple of years you have had a new ACRA (ph). That's me. A new deputy.

We've had three or four headquarter office directors come into ORA, four of four deputy office directors, five of ten headquarters division directors, four of five of our regional Food and Drug directors, 18 of our 20 district directors, and 9 of our 13 laboratory directors.

You're talking about a tremendous training need that we have to get at our new #cmpls, both management and our basic line employees.

With that in mind, we've been developing a virtual university for the

training of our staff into to get more rapid training to the individuals and also to reduce training costs, trying to bring them into specific locations. It takes time and money.

We've been working with the Office of Science to deliver training in conjunction with industry to get into new emerging science and technology issues so that our people understand what they're seeing out there.

At the same time, we have to have them sufficiently grounded in science so that they understand processes.

For example, they may be in Merck one day with a very sophisticated production technology. The next month they may be in a place in India or China where you're working at 1930s level technology, where they're still using old balances and whatnot to weigh out ingredients.

So they have to be able to transition between technologies.

We're also having to balance between our domestic and foreign regulatory

responsibilities, trying to make sure that we're covering both equally so that consumers are getting the best product possible.

We're having to deal with a tremendous influx or importation of goods now, and that means we have to do a better job of rapid methods, screening of products, so that we can get the best picture we can of products being entered into the country. We have tremendous rapid methods needs.

At the same time, we are on track with our laboratory consolidation as we move to consolidate functions and have better, more improved, more modern laboratories with better equipment.

We've added five pulse-field Gelve electrophoresis units over the last year so that we are capable of doing some fairly high tech analytical work.

We are moving towards laboratory accreditation, and we are moving rapidly to get all of our laboratories accredited.

We have been doing a check sample

program. We did 13 during FY 2000, and this was also included as a pilot study participation in the AOAC proficiency program.

We've been doing antibiotics sensitivity screening for Salmonella in order to generate data on the extent of antibiotic resistance, Salmonella in our food supply.

We've worked with CFSAN on this particular project and will continue to work in this arena.

We were instrumental in planning an implementation of the program in our Denver program. During FY 2000, we found quite a few, actually about 250,000 isolates, found several antibiotic resistant strains.

We've been putting on new workshops for our new laboratory directors in order to enhance communications, both amongst themselves and with our Centers. We put one together that was the first one that was designed as an interactive workshop with discussions focusing specifically on improvement of communication amongst labs, our various customers, and

development of processes to improve customer service.

We've been working, of course, on the dioxin strategy. As most of you know, we have dioxin as an issue. We've worked with our Arkansas Regional Laboratory to ramp up about 500 percent our analytical capability in the area of dioxins.

We've been active in the transgenic area and specifically recently in the transgenic corn issue.

Finally, we've brought our public affairs specialist into a forum to deliver a message on a national basis for FDA and we essentially will choose a specific message we want them to carry.

They do a number of things in dealing with the public at all levels, but we hadn't had a coordinated function in the past of trying to get specific messages out on behalf of the agency on a national basis.

We have ramped that up and that program is working well at this point in time.

And with that, I'll -- I've hit some very broad areas in a hurry, but I think I gave you a flavor for what's going on in ORA at this point in time.

DR. LANGER: Thank you.

Any comments or questions?

(No response.)

DR. LANGER: Steven.

Center for Veterinary Medicine

DR. SUNDLOF: Well, thank you.

The Center for Veterinary Medicine is responsible for all animal drugs and animal feeds that are used in the United States, and that includes things like pet food and feed for food animals.

I could give you an entire presentation that would last a day just on the issues that have come up through animal feeds, the most notable being the mad cow disease, the BSE issue. But there are all kinds of things that can get into animal feeds that are potentially hazardous to the public.

But I'm not going to talk about animal feeds today, I'm going to talk about some other topics.

The topics I want to highlight are the ones that I spend most of my time on.

(Slide.)

Antimicrobial resistance. Quantitative risk assessment, which is an area that we're moving into, and although it is an exciting area, trying to get the regulations to catch up with the new kinds of sciences is always an issue. And animal biotechnology.

The issue I spend probably most of my time dealing with is the area of antimicrobial resistance, and you've already heard some of the speakers talk about that.

(Slide.)

And our goal here is to ensure that significant human antimicrobial therapies are not compromised or lost due to the use of antimicrobials in animals, and this is a tough problem since antimicrobial drugs are very useful in animals, especially when they're

needed to treat infectious diseases.

So we have a real balancing act before us in trying to get a handle on where is the right balance between the needs of the animals and the needs of the public.

So we're looking at radically changing the way that we've approached it from a regulatory standpoint.

(Slide.)

First of all, we need a new framework to regulate these products based on their ability to produce resistance and pathogens that are important to humans.

We need an improved monitoring system.

We need to know what's going on out there in terms of the emerging resistance.

We talk about judicious use by veterinarians. Veterinarians have to use these drugs more responsibly to preserve them for animals and for humans.

(Slide.)

We're looking for alternatives to antimicrobials.

And we're investing in research in this area.

In terms of regulatory changes -- this sounds fairly bureaucratic -- Guidance for Industry, No. 78. I'm sure you've all read that. It was published in 1998, and basically it was an announcement to the United States that we intend to take a more aggressive approach towards the regulation of antimicrobials in food animals especially, and that we were going to start evaluating these products based on the rate and extent of resistance development and changes in the animal enteric bacteria that are known to be pathogens to humans.

(Slide.)

So that was our first wake-up call to the public that we were really going to get serious about this.

(Slide.)

Monitoring is the next area. Before we could regulate, we felt we needed a surveillance system out there. It was no good

trying to regulate in the absence of having good information coming back at you.

So we developed, in conjunction with the CDC and the USDA, what is now referred to as National Antimicrobial Resistance Monitoring System. It's a national surveillance program. It looks at human and animal isolates of bacteria that are pathogens to humans, and monitors over time the development of resistance.

Next. (Slide.)

This is kind of just a schematic of how it works, the Foodnet System, CDC's Foodnet System, in order to get samples from actual patients, and there are 8 to 10 catchment areas in the United States.

So you get a very good representative sample of humans that have been subject to food poisoning. They isolate the bacteria. They send them down to CDC in Atlanta. They run sensitivity screens on these various isolates.

And the little Petrie dishes down there at the bottom, the gray is Salmonella,

the red is Campylobacter; green is enterococcus, and yellow is shigella. So that's how I remember those.

And those are the organisms that we're currently screening for. And looking at sensitivity to 17 different classes of antimicrobials. We're using the exact same system for looking at animals.

And mainly we're looking at animals, carcasses of animals at slaughter.

Collecting the same kinds of organisms from them, and looking at resistance development to those same 17 antimicrobials, and by doing it in this way, we can see the relationship of the animals developing resistance to the incidence of human disease, which is resistant to antibiotics.

So this is extremely important. This is the core of our regulatory system.

Next. (Slide.)

So just a recap: NARMS is to provide descriptive data on the extent, temporal trends of resistance and enteric organisms from humans

and animal populations.

Next. (Slide.)

Judicious use is another area, and it's a program that has been adopted in the human medical profession, that there's a lot of attention now on education being directed towards physicians to use drugs in a responsible manner, such that they won't produce resistance.

We are doing the same thing for animals, and we're working with the American Veterinary Medical Association, actually funding some of their educational programs, and having each of the species specialty so the cattlemen and the swine producers and the chicken producers and the turkey producers all are developing their own judicious use guidelines and they're doing it specifically on a disease-by-disease basis so they have very specific guidelines that they're using now in order to preserve these compounds.

We're also looking at alternatives to antimicrobials, and the one that seems to have

most promise right now are competitive exclusion products. Mike Doyle knows much more about this than anybody else in this room, I'm sure.

But what these are are cultures of microorganisms, bacteria, primarily, that are administered to the animals by various routes. But they eventually colonize the intestinal tract of these animals, and they compete with pathogens like Salmonella, Campylobacter, and E. coli, so that the animal's intestinal tract is not colonized by those pathogens.

And these have a lot of promise. From a regulatory standpoint, they have some problems that we're trying to work our way through. We already have one of these products on the market and we hope to see a lot more in the future.

Research. In order to run these programs and have sound scientific regulatory decisions, we need to have good research, and we're funding intramural research and extramural research, and you can see some of

the things that we're funding there.

We're also working with NCTR and making sure that everybody knows what everybody else is doing.

But this is really important. When you look at the issues involved here, we just don't know how these microorganisms move through the environment, what animals are causing the predominance of infection. Some very basic issues, basic scientific issues, that we just don't have good answers for right now. So research is very important to us.

(Slide.)

The next area that I want to talk about is quantitative risk assessment.

We actually conducted our first and finished our first quantitative risk assessment. And I'm a true believer now. Where it can be done is a wonderful tool. You have such a clearer idea of where the risks actually lie and where you need new data. It's just a wonderful tool.

They're hard. They're very difficult

to conduct, and I'm glad to see that National Science Foundation is investing in some research, because I think this is a really productive area.

We did our quantitative risk assessment on Campylobacter and resistance to fluoroquinolones. So doing microbial risk assessments, and CFSAN is also doing these, it's harder, I think, than the general toxicology chemical type risk assessments.

But I think they will really pay off well in the future.

One of the problems that we have, though, is in the communication. Communicating ~~to the public~~, when we go from a "your food is safe" standard, to "your food has a probability, some certain probability of risk."

It doesn't really fit into our regulatory standards as they are written right now, and so as we make this transition from the safe to the 'some certain probability of risk,' it's going to be challenging and it's going to be challenging to get the message communicated

to the public.

But I feel fairly certain that that's where we're going to go. When you look at our international trade agreements, you look at the codex alimentarious, it's all based now on risk assessment.

World Trade Organization. World Trade Organization under the sanitary, Phyto-sanitary agreements, calls for, in the case of trade disputes for risk assessments. So we're going to be seeing a lot more of these.

Next. (Slide.)

The one that we've done recently is to assess the human health impact of fluoroquinolone restraint Campylobacter infections associated with chicken consumption. And we used a data that came out of our NARM system plus case control studies, plus a lot of other information. And all that is available.

Next. (Slide.)

Is available on our web site. We just published the final version last month, and it's a very interesting document if you are

interested in risk assessment.

Next. (Slide.)

We're in the process of conducting our second microbial risk assessment, and that's to look at vamyacin and causing resistance to Synercid, which is a new drug. It's the drug of last resort after the drug of last resort. Vancomycin is no longer effective in treating patients with enterococcal infections in the hospital.

This drug just came out about a year ago. The analog of that drug in animals is vancomycin has been on the market for approximately 25 years and was passed over as a human medication. But because of the increasing resistance seen in vancomycin the drug companies went back and found this drug to be effective.

Now we have a problem, potentially, with the continued use in animals.

Next (Slide.)

The next area I want to briefly discuss is regulating products of animal

biotechnology, and there are basically two forms.

Biopharm animals, those animals that are being raised, for instance, goats, to produce pharmaceutically-active substances in their milk, which then get purified and are used as drugs or vaccines.

That's one of the areas.

The other area is agricultural biotechnology. And that's producing animals that grow faster or disease resistant or have other characteristics that generally serve an economic benefit to the agricultural sector.

CVM is dealing with both of those issues.

(Slide.)

We decided on the Food and Feed Safety. So all of these animals that are being used for biotechnology purposes, even the ag -- or even the biopharm animals, have to go someplace when they are no longer useful. And we have to make the decision whether or not those animals can be used for human food or for

animal feed.

Generally, at this point, we have not allowed either of those things to occur, but in the future as there are more and more of these animals out there, we're going to have to make some decisions on the safety of those animals in the food supply.

Animals of biomedical research are generally not considered safe for use in feed.

And the other issue that we're going to be dealing with and are dealing with are the environmental issues.

What about the vectors that were used to create these transgenic animals? What about the potential for escape?

And we regulate these on a product basis not by process, unlike the European community, which has a general concern over biotechnology rather than looking at the individual products. We try and look at the individual products and determine whether they're safe, regardless of the method by which they were produced.

FDA believes regulatory authority for products of genetically-engineered animals may already be in place.

Under our laws, under the Food, Drug and Cosmetic Act, it says: "Articles other than food intended to affect the structure or function of the body of animals is an animal drug," and if you insert genes into these animals, then you obviously change the structure of those animals, and the genes are generally inserted to produce some altered function in the animal. So you've met both of those criteria.

So animals that are transgenically modified, then, are regulated as animal drugs, and supposedly should be going through CVM for review.

I noticed that NCTR is creating transgenic mice, and I've asked Dennis to initiate a seizure action immediately.

(Laughter)

But we're going to have to be dealing with these issues in the future.

(Slide.)

Here's kind of the poster child. And you've heard about it already, and that's the transgenic salmon. These salmons are siblings. They're the same age, except one was genetically modified, and that's the top one.

And you can see that the -- this is an almost irresistible technology. Once you have the ability to do something like that, how do you stop something like that.

So we're trying to be very careful. We do have this particular salmon under review as a new animal drug right now. We have numerous challenges, many of which are, what happens if this animal escapes into the wild? How does it compete with wild species?

Because of the genes it may have survival characteristics that exceed the range of wild-caught salmon.

So there are lots of issues that we're dealing with in the area of animal biotechnology, and we're just at the very early phase of that, and we think there's going to be

an explosion in this area.

We have other animals now that are under review, but looking at knockouts, clones, all of these new technologies are going to be issues that we'll be dealing with in the future.

I think I'll stop there and ask for any questions.

DR. LANGER: Questions?

DR. SCOLNICK: I have one just because you're into this subject.

Has anyone tried to make a cow without endogenous cow (inaudible).

DR. LANGER: Could you maybe repeat the question for everyone?

DR. SUNDLOF: Yes. Has anyone tried to create a, I guess it would be a knock-out, pryon cow. Not that I'm aware of. Maybe somebody else has better information on that.

DR. SCOLNICK: My understanding of the science is if you don't have the endogenous pryon you can't be effective. That's what it seems to me. I don't really understand why no

one tried to do that or why an agency is not trying to foster that to get rid of the whole problem.

DR. SUNDLOF: That's a great thought.

Greg.

DR. ANDERS: Steve, I don't know if it's possible by conventional breeding techniques to create a mega-salmon. But if you did, would you regulate it?

DR. SUNDLOF: No. Right now, we're trying to parse out where it is we actually want to regulate our regulatory authority. I really don't want to regulate your transgenic mice.

(Laughter)

I'm probably not that interested in ornamental fish. There are activities going on.

And I'm not really interested in conventional breeding that leads to these kinds of increased productivity.

And then we get to another area such as what about clones? Should we be interested

in animals that are cloned because that's the new technology that's going on now.

They're selecting the best genetic stocks of animals, cloning those animals and using those as parental and grandparental stock for raising animals, and we know this is actually happening.

And should we be worried about that? So that's another area.

What happens with the no-takes or the partial takes? What do we do with those animals? Lots of interesting questions.

DR. NEREM: Just to follow-up. So conventional genetic modification through the breeding is not regulated. At what point do you step across the line?

DR. SUNDLOF: That's the question. At what point in all of the manipulation that can go on does FDA step in? We're actually going to be working with the National Academy of Sciences to help us and give us guidance on where is the public protection needed and where should FDA be regulating.

DR. NEREM: When is a GMO a GMO.

DR. SUNDLOF: Yes. When is a GMO a GMO.

DR. LANGER: Mike.

DR. DOYLE: Steve, it seems that the environmental issue is one of the biggest issues regarding the fish anyway, so how does FDA get into that? Would that be more of an EPA issue?

DR. SUNDLOF: Yes. That's a question that we hear quite a lot. Why is it FDA that's regulating the environmental aspect? Actually, FDA regulates under the National Environmental Police Act, NEPA. We have authority to regulate, and we do for drugs. For the animal drugs that we approve, we require an environmental impact assessment.

Some of those things are huge. When we approved another one of our controversial products, BST, we even looked at methane production as it might cause greenhouse effects.

We looked at needle disposal and

everything else.

So we have experience and we have staff that is trained in this area, but we are working closely with National Marine Fishery Services and Department of Interior, and the EPA, and this is actually going on at the White House level, to make sure that we're asking the right questions and getting the right answers back on this. So it's a multi-agency problem.

DR. LANGER: Bob.

DR. NEREM: I have to pass this on. Greg just made a comment to me.

Apparently genetic modification by trial and error, we don't regulate, but when we know what we're doing then we will regulate it.

(Laughter)

DR. DAVIS: That's been one of the issues, the concern for -- concern about genetically-modified food. Farmers have been modifying food for hundreds of years and we haven't been regulating that. So why is laboratory-modified food uniquely different than PhARMA-modified food?

And if you take that analogy, we have the same thing with breeding salmon to look like them and they're getting out versus genetically modifying salmon and having them get out.

DR. SUNDLOF: And, in fact, there's a tremendous amount of environmental pressure, just from raising domesticated salmon, getting out and competing with the wild stocks. That alone is a huge problem.

DR. LANGER: Others? Yes?

DR. FENNEMA: A comment about this quantitative risk assessment and your concern that the public might not accept this.

Would not a good model, which is a precedent in my mind be the 12-D concept that's been used for years and years and years for sterilization of canned food?

DR. SUNDLOF: I'm not familiar with that.

DR. FENNEMA: Well, it is a probability approach to sterilization from that, which is you've got all kinds of physical

evidence of billions and billions and billions of canned foods where this has worked. So it might be something for you to look at because it may be a useful tool in convincing the public that this works.

DR. SUNDLOF: Thank you.

DR. LANGER: Probably we should go on. Kathy.

Center for Biologics, Evaluation and Research

DR. ZOON: Thank you. It's a pleasure. Now that Steve got everybody all charged up it's a good time to come up here.

CBER has had a very active interest in a regulatory research paradigm since our origins, and in fact, for those of you who may not know we started back in the NIH and it wasn't until 1972 that we moved into the FDA.

So we have very strong ties to the NIH. We're located on the NIH campus and our research labs, as well as very strong ties to the CDC, because many of the products we regulate have public health importance beyond just what FDA does.

So it really needs to be a very integrated program with the National Institutes of Health, the Centers for Disease Control, and the FDA.

So many of the issues that I'm going to describe, which are scientific priorities, have actually been focused on our regulatory mission in regard to the effects of these important issues on CBER's research program.

Now in saying this, CBER uses both for lab and non-lab a research-reviewer model to address the question of how do we integrate the science into the regulatory paradigm?

Well, the same people who are doing bench work also do the reviews or the same people doing new statistical modelling are the same people who review application, and we believe this is a very effective way at integrating science into your programmatic and regulatory responsibilities.

Recognizing the resource limitations we've had over the past several years, it's been a real challenge to maintain this program,

and we have supplemented our program in a number of ways through various leveraging activities.

One is working with the NIH on interagency agreements.

Another way has been working with DARPA and DoD, extensions of various grants on these areas. CRADAs with a number of companies to deal with some of the scientific issues. The National Vaccine Program has been another.

Actually, our scientists apply for research grants.

So with that introduction, I'd like to now go into the research priorities.

Vaccine safety is a major research priority for the Center for Biologics, and this way it encompasses both existing vaccines that we have today on the market as well as looking for the opportunity to facilitate the approval of new vaccines as well as improvements in vaccines.

In particular, those areas right now are focusing on several points.

One is adventitious agents, which is key. We don't want anybody to get infected with something they don't think that's in the product that shouldn't be in the product.

And to do this, we have started establishing a microarray program looking at developing microarray chips for adventitious agents, and screening vaccines.

This is in its infancy, and we've just recently been awarded a DARPA grant to facilitate this program as well.

The other area is looking at new cell substrates for production of vaccines. Using continuous cell lines has always been a controversy in vaccine production, and this is an area that we would like to see move forward and we think good science behind looking at this will facilitate the production of vaccines in this area.

We also have the new areas of vaccine production looking at new types of vaccines for herpes, human papilloma viruses, et cetera.

And understanding the pathogenesis of

these diseases so we can have good biomarkers for efficacy is very important and to integrate these programs and the understanding of our scientists that review these vaccines are critical to doing a good job.

In looking at blood safety, this is another very important area for us. Clearly, the safety of the blood supply is paramount. Looking for new and approved methods of assuring safe blood and blood products is critical.

This is also expanding into the tissue area, and one that we are currently engaged in setting up new programs in.

So what are the areas that we want to focus on here? And much of it involves nucleic acid testing. This is extremely important in looking at increased sensitivity, specificity, and reliability, of tests for adventitious agents.

Again, not only are we looking for things such as HIV, HCV, HBV, but also looking at for more nuisance agents like parvovirus

B19. We're also on the lookout for new agents that may infect the blood supply, and we have a collaborative effort with the CDC as sentinel.

If there are new agents coming into detection, that we have a joint group that works on that and then works on developing the tests that might be needed to roll-out to apply to the blood supply.

But I think these are areas of high specificity and specificity and sensitivity.

Steve pointed out, and a couple of you also mentioned the issue of TSEs. And this is, again, a very big area for both the vaccine and bloody area.

TSE agents, BSE, has clearly been in the minds of a number of policies in this area, but we are working very hard in our laboratories to develop new methodologies for validation for removal of TSE, detection methods for TSE.

We're hoping to use both microarray and proteonomics to help facilitate those studies, as well as new diagnostics.

So this is an area, not only have we been working with in a national level, we have also been very much engaged in these issues with the WHO and I think have had a lot of productive, collaborative efforts in that area as well.

The next overhead points out, or third area, which is dealing with therapeutic product safety. This has become increasing important to our Center with the advent of new technologies, whether we're making products from transgenic plants.

Steve mentioned already the issue of sourcing material from transgenic animals. If they're biological products, we would regulate those as biological products, subsequent to their introduction of producing either these products in their milk or in various other body components.

So this is something we're looking at very closely. I think the ability to set up new policies and new guidance needs to be based on sound science and understanding of the

critical issues.

Again, adventitious agents. You're going to hear that in almost every product line we have because that's a key issue for us to maintain public confidence and public health factors.

So that's another area.

Xenotransplantation is another area, looking at potential sourcing of animal organs or tissues to help supply critical tissues and organs in the absence of human organs and tissues is critical. Again, adventitious agent testing is key.

We've had a case with porcine endogenous retrovirus recently where CBER has actually developed the tests that are now being used to analyze those particular agents in various porcine products.

So these are areas. Again, some of our challenges both now and in the future are going to be stem cells; using stem cells to create new tissues, as well as the appropriate standards and controls.

We need expertise in developmental biology for such things as areas in assisted reproductive technologies, as well as understanding cellular differentiation factors.

So we're in the process of trying to recruit a couple of people in this area to have at least a core that we can then leverage with the scientific community. We're also working very hard in that area with the National Institutes of Health to establish those types of criteria.

In addition, gene therapy is continuously on the horizon. We have an advisory committee on right now looking at what are the types of science that needs to be done to assure vector safety as well as improving preclinical animal models for assessing vector safety.

Again, we work very closely with the NIH and the RAC in order to elicit these and have a very robust program with respect to this area.

The next area that I would like to

focus on briefly is counter- and bioterrorism. We've had a very active engagement with both the Department of Defense for vaccines for such agents as anthrax.

We're also concerned about issues of having appropriate vaccines for plague and various other viral agents such as smallpox and equine encephalitis viruses. Also things such as toxins -- Botox and other types of toxins and other bacteria as well.

We have had some limited resources that have been given to us in this area. There's a lot more work to be general. Clearly, there's a public health need, and both a military need for these types of agents as well as immunoglobulin products that we also regulate at the Center.

Last as a priority is new approaches to clinical trials and adverse event evaluation.

(Slide.)

This is an area where we think a lot of emphasis needs to be placed, whether we're

looking at new designs for vaccine trials, looking at new ways to detect low frequency adverse events, whether we're looking for new ways to do product approvals with respect to examining superiority or inferiority type of trials.

Looking at new methodologies, especially with respect to statistical approaches. All of our scientists are engaged in these types of processes to see that if we could find the very best models to look at, getting the most out of data, new issues with respect to data mining, for looking at vaccine safety and adverse events, as well as looking at new areas for improving health-related quality of life indexes, particularly in cancer patients and applying those to clinical trial designs.

So this is just a very quick snapshot of our priorities.

At the end, what do we hope to get out of this research? What's the bottom line?

And the bottom line for our research

and the hopeful outcomes of our research will be decreased adventitious agents and these products are elimination all together.

Decreased adverse events that are experienced by people taking biological products.

Increased product quality.

And an increase in our guidance to industry so that product development could move forward, especially in new technology areas and improve methods and standards.

Thank you.

DR. LANGER: Thank you.

Any specific questions?

(No response.)

DR. LANGER: Bob.

Center for Food Safety and Nutrition

DR. BUCHANAN: Thank you. I think I'll sit here.

First, I'd like to pass on a message from Joe who extends his regrets for not being able to be here today. And hopefully I'll do as good a job as he would normally do.

I'd also like to indicate that one of the innovations that Joe put into place not long after joining CFSAN was our annual priority document that we put out on the web and we send to all of our stakeholders that we update yearly that lays out the list of items that we put on our "A" list.

These are the things that we intend to put out each year and accomplish, and then we have a report card at the end of the year that reflects back on how much we've actually achieved during that past year.

The new priorities document is just about to come out so we'll make sure you all get a copy of it when it becomes available.

Likewise, at that same time, we'll publish our report card for this past year.

Also accompanying that is we have through the Office of Science within CFSAN, we publish a regulatory research needs document. Now that did come out in July. It's been circulated to most of the professional organizations.

It's been circulated to all of the federal funding agencies and to anybody else we can think of that has money or researchers. This has proven to be a very successful means of leveraging.

Our estimate right now is that just simply was one funding agency. We've been able to secure approximately $13.5 million on FDA regulatory research needs just by providing what our priority needs are.

So in light of the limited time, I do want to just pick up a couple of items and discuss them briefly that I thought you would be interested in from our Priorities document, and probably the most important that's going to be impacting us directly this upcoming year is that we're moving. And this is going to be taking a substantial amount of our time.

With possibly the exception of our Gulf Coast seafood laboratory in Dolphin Island, Alabama, pretty much everyone else is moving at some point this year. We'll be moving from downtown out to the College Park