facility.

In large part at the recommendations coming out of our peer review that the Science Board oversaw, we have had a major reorganization at our Mod I laboratory. We now have the establishment of our Office of Applied Research and Safety Assessment.

And in addition to that, we'll be undergoing a major renovation at that fact to strengthen both our nutrition program and to strengthen our toxicology program.

I might note here in something that you can help us with in the upcoming year is we will be as part of that reorganization recruiting a new director for that office and a lead scientist for toxicology. Both of these are scheduled to be SBRS level positions. So we're going to be looking for some really senior people to help us strengthen and bring into fruition some of your recommendations.

I'd also like to mention that this is the third year of the Presidential Food Safety Initiative Program. This has been a very

highly successful program in terms of both regulatory and science issues, and that would be expected since our research program is intimately integrated into our regulatory program.

In that regard, we have a great deal of work to accomplish this year in a number of important areas. Just to identify a few of them, we continue to work for implementation of HASUP both in terms of implementing our seafood program and getting our juice acid rate in a final form.

We have initiatives in the area of egg safety, proto safety, sprout safety. Each of these are both major regulatory initiatives and scientific issues as we support those activities.

We were called upon by the President this past summer to accelerate our activities in the area of listeria monocytogenes, and this is both a very strong research and regulatory initiative.

We have continuing activities in the

area of antimicrobial resistance. Many of them are in close coordination with what's going on at CVM.

We have also had an ongoing activity in the establishment of good agricultural practices for reducing food safety concerns.

We've also had a number of issues that Joe talked a bit about when he met with you the last time you were together.

We have ongoing activities in the area of dietary supplements, and we are very pleased to see that we have been provided additional funds in this year's budget to establish a collaborative program with the University of Mississippi's Center for Natural Products Research, and that will be initiated in the upcoming year. Certainly it is a very high priority area.

We've seen, as Liz said, the recycling of a number of issues, too, that we're going to be taking a substantial amount of our time in the upcoming year will be methyl mercury and dioxin, two that have surfaced once again after

lying dormant for a year or two so we'll be devoting quite a bit of effort there.

And also one that has obviously been in the papers a lot is GMO Foods and how do we assess the safety of these products and appropriately handle them in the marketplace.

A second area I'd like to bring to your attention is to reinforce some of the comments that Steve made in the area of risk assessment.

Risk assessment, while we've been doing it in the chemical area, microbiological risk assessments have come to the forefront. We have increasing activities in trying to integrate those two together because many of our risk assessment resources that we use for microbiology are tied up with our chemical risk assessment activities.

So we have now a very scarce resource that we now have to be able to set priorities on in terms of where are we going to take our scientists and devote their time and energies.

This is also -- this is where success

has generated its own problem. Certainly in the area of both food chemical risk assessments and in food safety microbiological risk assessments, FDA has acquired an international reputation as being the leaders in this science.

We are called upon to assist on an international basis supporting both WHO and FAO in international risk assessments through JCFA (ph) or the newly formed ad hoc consultations on microbiological risk assessment.

So we're trying to balance our international commitments with our own limited resources.

Just to give you an idea of how heavily we are involved in these international activities, Steve did mention codex alimentarious.

But based on my last count, 14 of the 18 codex alimentarious committees are headed, the heads of delegations, are FDA. So it's taking on an increasingly important role.

We have, as one of our priorities,

restructured our Advisory Committees within CFSAN, expanding them substantially. This will be a challenge for us to get the best that we can to serve on these advisory committees, and I know that you have all been tapped here. So any of your recommendations of who can help us in our areas of both our General Advisory Committee, Biotechnology Subcommittee, Contaminant Subcommittee, GMO Food Subcommittee, and Dietary Supplements, we're very much looking for the best and the brightest to serve on these, to help us through some very difficult scientific issues.

I might note, also, as a developing area that's going to take some priority considerations is in the budget language. There has been some changes in the National Advisory Committee for microbiological criteria for food.

This is an interdepartmental committee that we relied on heavily to bring our microbiological issues forward.

There is going to be a restructuring

of that committee, and in the meantime we are probably going to have to expand our own Advisory Committee to deal with many of the pressing microbiological issues.

So, again, we are going to be looking for your help.

A couple of other areas that reinforcing the comments of the Center directors, assessing safety, continues to be a major thrust for us. Two of the areas now that we're spending a lot of time on is how to effectively assess the safety of allergens, particularly in conjunction with GMO foods, and also improving our adverse event reporting.

Another issue that was mentioned earlier but is taking increasing importance is the validation of methodology.

We have the need to have methods that have been validated to the appropriate extent. On the other hand, very often as we respond to either regulatory or public health concerns, we have the need to rapidly validate methods as we have to deal with the thousands of different

food matrices that can be involved.

So this is going to be very much of an issue.

And then the final one that I'd like to mention as a priority area is the areas of tracebacks and investigations. One that we work very closely with, ORA with.

Again, this is one where success brings its own problems or new challenges. During the past years we've worked closely with CDC to get things like Foodnet and Pulsenet on line and accepted around the country.

In the past, it used to be that food-borne disease, we'd say that about 60 percent of food-borne disease was untraceable. Well, during the last couple of years because of things like Pulsenet, many of those small outbreaks that were scattered around the country, we now know that they are outbreaks and we could begin to trace them back.

And that's increased tremendously the burden on our people that are involved in public health outbreak investigations.

And, again, we're looking for new ways of how to handle tracebacks, new ways of how to take the information that we're getting as a result of these tremendous improvements in surveillance.

All those, informatics, and proteonomics and genomics, all that is bringing us to the point where now we're learning the answers to questions that we've never been able to ask before, and we have to find new ways of being able to investigate those and find out the sources of the problem.

So I hope I've given you an impression that we're going to need your help. We have a tremendously large menu to select from this upcoming year, and we're looking forward to working with you to find ways of dealing in new ways with the ongoing problems we have.

DR. LANGER: Any specific comments or questions?

Yes.

DR. DOYLE: Bob, the standard methods that the Agency's been using for years has

traditionally been cultural procedures. With PCR and all these more advanced and available to us, will the Agency soon be adopting those methods routinely for the industry to use as markers, if you will?

DR. BUCHANAN: Mike, if you go back and look at damage, every so often it's updated. In the latest edition we have an increased number of methods that are what we'll call the classic rapid methods.

Certainly the validation of those and the ongoing validation as manufacturers, commercial kits, modify their protocols as a challenge to us.

But I would say that many of the standard methods that we currently use in our programs, both within CFSAN and in the field are increasingly relying on things like PCR technology or immune technology.

So, for example, our ability to conduct an international survey for Shigella for the first time, because we always knew that Shigella was in foods, we just didn't have a

cultural method that was effective, for this past year we've been able to include a survey of produce because we had a PCR method that now has become sort of the standard for the Agency.

So, yes, we use the best as we can, understanding that these methods do have to be validated to the point that we can use them for regulatory concerns.

DR. LANGER: One last presentation, David, and then we'll take a break.

DR. FELGAT: Thank you. I actually have your ears for a little bit longer this afternoon so I'll keep my remarks focused on some of the hot topics.

Actually, I decided to select them in an arbitrary and capricious manner. I picked the topics that we asked Congress for money for --

(Laughter)

-- and that they actually gave us money for, and not every year do they give us money for specific topics.

Last year, for example, the funds were

all earmarked for faster product review, but this year they actually earmarked money for genetic testing, the reuse of single-use devices, development of standards, and then we received some money as part of larger agency efforts in the area of bioterrorism and antimicrobial resistance, and I won't say very much in those latter two areas.

But I think that the first three actually illustrates some of the challenges and how the science intertwines with regulation.

The genetic revolution has already been talked about by many people here, and the issues for the Center for Devices range from topics dealing with developing the diagnostics that will be used with pharmacogenomics;

The very rapidly expanding area of genetic testing of humans for genetic traits, and,

Then there are many nonhuman genomic examples. In fact, you were just asking about one of them which is the applications of genetics in the microbiology rapid diagnostics.

If you take a look at the way the genetic tests developed and what the challenges are, you'll see how this interplays with the regulations.

Historically, genetic conditions in humans were found typically by looking at the biochemical markers that the disease created so tests for cystic fibrosis, tests for Tay-Sach's disease existed before we had any way of directly tapping the genes; in fact, probably before we knew exactly where those genes are.

Those kinds of tests, historically, have been produced as kits. They've been regulated as in vitro diagnostics, approved by the FDA and used broadly.

What's happened with genetic testing that's based on actually tapping the human genome is there's been an explosion from a few hundred tests a few years ago to now, over a thousand that are listed as available in the NIH's database of human genetic tests.

The interesting thing about these

thousand genetic tests is that not even 10 of them are traditionally developed in vitro diagnostics. These are all offered as services by individual laboratories.

In fact, the majority of them by university laboratories.

The methodology, the test itself, does not travel in interstate commerce, if you will. The blood travels to the laboratory, and the information is returned as a service.

And the complexity of the issues around genetic testing and the question of why should something as important as the information from genetic testing, which unfortunately is bad news. There aren't that many genes that you can tape into that tell you something that you really wanted to know that was good.

The issues of informed consent, the issues of population screening, the issues of discrimination, have led the Secretary, Dr. Shalala, to form a Secretary's Advisory Committee on genetic testing to explore these

issues, and one of the strong recommendations of that group is that these tests actually require oversight, and the ability of the regulatory process to assure that these have the same consumer protections that we do for other in vitro diagnostics.

But the thing that we have to say as a starter is that we can't do business as usual. Normally, in a typical year, we might have a dozen or so novel tests that are regulated with premarket approvals, and to actually look at a thousand novel tests and look at the volume of applications and the kind of evidence that's required and the challenges with some of the conditions which are rare.

We've been looking with other agencies and in the public forum to actually develop a paradigm to phase in the regulation of these tests that's based both on the science of how they're conducted and also the public health needs.

But then of course when we look at these tests we realize that other technologies,

such trip (ph) technologies and snips (ph) and many of these things may make some of these technologies rapidly irrelevant, and it's going to be a real challenge for us to keep up.

As Dr. Woodcock mentioned, one of the real fundamental questions for us is how do we obtain and manage expertise and what's our role and what's the role of other groups.

In this area, we've tried to leverage our own expertise by working with many of the societies that deal with molecular clinical pathology, that deal with genetic testing, and patient groups that are advocates for this year.

We switched to the re-use area. Genetic testing is a high-tech area. Re-use must be a very low-tech area. You're essentially talking about washing off and cleaning things and using them over again.

But, in fact, re-use is actually every intertwined with all of the high-tech developments in device development because the types of products that there's the most

economic incentive to re-use are the expensive, difficult to manufacture.

Often, things that have used miniaturization and have used complex material such as new plastics or new coatings.

And the ability to be sure that these products will perform after a hospital has cleaned them is a key area.

We began to get concerned about this area a couple of years ago as we saw more and more products that looked like they'd be very difficult to re-use, and our own laboratories began a collaborative project with Walter Reed Hospital to look at devices which had been used and what were their characteristics and how have they changed, and in what ways were they not -- what types of things were likely to be unsuitable as a starting material to remanufacture a device.

We've had to put forward a paradigm of how we would deal with this problem. It has some parallels in terms of the regulatory challenges, just as the home brew of the

University laboratories doing their own genetic testing gives us five or six thousand new manufacturers we've never had to deal with before, if we look at all of the high complexity, clinical laboratories capable of doing this.

Re-use gives us the challenge of dealing with the hospitals and surgery centers. Again, another five to ten thousand institutions that perform these practices, and how do we make sure that the devices that are used in these centers are of high quality?

We think that our role, actually, in the laboratory stimulated much of the work which has now been picked up by industry, which has been picked up by some of the third-party reprocessors, and by some of the original equipment manufacturers that want to demonstrate why their products are appropriately labeled as single-use medical devices, and this is an area, in fact, if we did not have the ability to identify what the scientific issues were, it would sound more

like arguing over technicalities about whether something is labeled a certain way, does it have to be used a certain way, and what are the legal requirements and liabilities.

The third area that I would like to just touch on very briefly is the whole area of standards and standards development, and interestingly this was even labeled on the budget as science development.

The Center has had a very strong commitment to working with standard-setting organizations.

We have members on the Board of Directors of ANSI, NCCLS, ASTM, and we participate in many of the ISO committees, including the committees that are looking at the revision of ISO 9000 and the series that are sort of the underpinning for the requirements you need to get a CE Mark for approvals in Europe.

So we take this very seriously. And as part of the changes that occurred in the Center's re-engineering program, some of it

codified in the modernization act, we have incorporated the standard's process into the regulatory process.

You know that FDA's motto historically has been "In God We Trust, Everyone Else Sends in Data." In the Center for Devices, you also can substitute conformance with the standard where a standard has been recognized for sending in the data that showed you are accomplishing the same thing that the standard has been accepted for.

And we've had a process of identifying and recognizing standards to assist not just in the application for new products but also it's used in the third party program, the third party review program; in programs such as mutual recognition efforts which are slowly coming along and in many of the international harmonization efforts.

So the standards movement has had a very important role.

Often we're in the position of evaluating the standards and the basis for the

standards that's worked with the others. In fact, that's the majority of the cases.

But there also are times where, in fact, our laboratories provide the data that are used by the standard organizations in order to set the standards.

And, obviously, we tend to pick the things that either strongly affect medical devices or affect the radiological health.

So this is kind of a -- just as this morning has been kind of a potpourri of issues, we could actually go on about a dozen others, but I thought I would at least begin the discussion with three areas that Congress has funded.

We have all the same issues that the other Centers do, which is how do we deal with managing expertise.

How do we attract it, how do we maintain core competencies. How do we teach people that their job is to find the expertise they need to make a science-based regulatory decision.

That may be within the Center. That may be tapping resources within the Agency. That may be extending out more broadly as other Centers do to the NIH, to the Center for Disease Control.

That may be using our academic collaborations and other efforts.

The culture that we want to build in the Center is a culture that recognizes that this is a science-based endeavor, that this is science-based and evidence-based regulatory decision-making, and it's the scientist's job to bring the best science to bear on the issue.

Sometimes that will be from their own core, expertise and competencies, but other times there will be a contractor of knowledge, if you will. It will be their job to make sure that we have the information and background to make the decisions.

So I'll be coming back to some of these themes this afternoon, so let me stop now. If there are questions, I'll be happy to

take them.

DR. LANGER: I think what we'll do is we'll take a 15-minute break, and then we'll come back and we can discuss specific points and then of a more general discussion we'll put on a slide to help focus that.

Why don't we take a 15-minute break.

(Recess.)

DR. LANGER: One comment before we get started, and I wanted to put that slide up. If everyone could activity their microphones before they speak, that would be good.

I was just checking to see that I had done my job.

So why don't we get started.

I wanted to put a discussion slide up.

Before we start on that, were they comments, specifically, or questions on David's talk?

DR. SCOLNICK: I wondered, given the huge volume of genes that are being sequenced, identified with disease, and the kind of

logarithmic pace of that, what is it that you actually propose to regulate, specifically?

I see this as a rather formidable problem, and I wondered, since your comments were general, what is it that you're actually suggesting that you're going to regulate?

DR. FEIGAL: I think it depends on what the claim for the genetic test is. If it's detecting the gene, then it's comparable to other kinds of diagnostics where you're dealing with the accuracy of the -- the analytic accuracy of the test.

If you claim that you can predict development of breast cancer because you've detected the gene, it's not just enough to say that you've accurately detected the gene.

So those are probably the two extremes. There's some genes where the information that it conveys is very straightforward, and in fact how to even work with that information in the community is very straightforward.

Like, for example, sickle cell.

That's something that if the technology for detecting that gene changes and improves, that's a relatively low standard. But at the other end, we're probably looking at needing to have clinical follow-up information, and then there's everything in between.

DR. SCOLNICK: If a university lab today tests a patient for Huntington's disease gene-related information with the complexity of what that means with regard to the length of the glutamine repeat, what is it that you would regulate, given what a university lab would be able to say to a patient, having done a precise molecular experiment?

DR. FEIGAL: Well, there's been an attempt to sort the tests by the characteristics that makes them either at -- the information at high risk or puts it into a lower-risk category.

One of the other factors is the rarity of the condition, whether or not we're dealing with rare diseases, and the ability to make the diagnosis with other kinds of information that

supplement the particular test.

So, in fact, the Secretary's Advisory Committee has actually been struggling with an algorithm to divide the tests between those which would rely mostly on analytic accuracy versus those which would require clinical information and clinical follow-up.

The situation where it's a rare gene that's a familial gene, not seen very often, is obviously one extreme.

We're using a gene for population screening or newborn screening or for making a reproductive decision, then that puts it in a different category.

But the issues you raise in terms of the volume of information and the amount, just starts when you look at the thousand universities that have genetic tests.

When you think about the paradigm of evaluating a gene chip, which might have a thousand tests on the gene chip, and you think of the normal way that you evaluate even analytic specificity, you have a set of

reference samples for a specific piece of information.

And now if you have a chip that wants to simultaneously assess 10,000 pieces of information, we won't be able to address that in the same way. We're not going to be able to say that you've got to go point by point, and those are the issues that we need to discuss.

This is still a work in progress, and in fact we have an advisory panel on genetic testing that will meet with us to publicly discuss these issues and get feedback. And the Secretary's Advisory Committee has been a public committee that's discussing this.

DR. SCOLNICK: I guess you know what I'm getting at. If I'm a physician and I have a patient with Huntington's and they want some test done or it's appropriate to do some test to try to assess the risk in another family member or an unborn human, potential human, and I find that there are 38 repeats or 42 repeats, are you going to try to write regulations which are going to govern the words I use to describe

the implications of that data to that family?

And are you going to try to do that now for all of the genetic markers that are going to exist for all of the diseases that are going to have genetic predispositions as the genome information rolls out?

I see that as an impossible task.

DR. FEIGAL: Well, there are some common elements, and this actually comes back to where we leverage off of other groups.

If you look at the setting of the issue of informed consent for familial conditions, there's some common threads that come across that.

For example, if you're looking for a carrier state and you detect it in a child and the issue has actually been brought up for Huntington's, what do you do in a situation where a Father who has it on his side of the family doesn't want to know if he's going to develop Huntington's, but the wife wants to know which of the children are at risk?

But if any of the children are found

to have Huntington's, you have just unmasked him.

So the whole issues of how to do that are things so that where we see the role and where we see the partnerships with the genetics groups is for them to develop prototypes for common clinical scenarios with genetic information for how to deal with these situations, for how to deal with what should be the standards for genetic testing.

At the other end of the spectrum, the CLIA regulations, the Clinical Laboratories Improvement Act, requires that if information is going to be used clinically, it be done in a high complexity laboratory.

That's probably not even the case now for all genetic tests. There are probably some of these that are being done in research laboratories that do not meet the requirements of that act.

There also have been situations where laboratories have had to recall and try to contact thousands of patients who have been

screened because they found that the test didn't have the sensitivity that they thought they did, and they informed patients that they were not carriers for a condition, and then were notified the fact that they were when they had a child with the condition they were trying to avoid.

So there are a whole series of complex layers. I think what works in our favor is, although, there are thousands of genes in genetic informations, there are some common themes and some common threads, and rather than treat these all individually which would swamp us and would slow and make us the roadblock for all of us, we need to look at the way we solve problems, a chunk of information, have the right regulatory tool for the problem we're trying to deal with.

Right now, for example, many laboratories don't appear to have a way of tracking the errors that are reported back to them in their testing. And that's just one of the standard things that's expected of a

regulated in vitro diagnostic, whether it's approved by CLIA, the State of New York, or by us.

So it'll be a process where we'll need to phase these in, but the issue of the multiplicity information is one we've thought a lot about. It's a real challenge.

We're not going to be able to do it the way we've always done it, and we need to find the ways that -- we introduce this in a way -- I think part of the challenge is to introduce it in a way that we don't lose the public's trust.

They're very skittish about information, about who's going to use this, who's going to have this, particularly when many employers are self-employed so your employer carries your health insurance and you order a diagnostic test and it goes back to your employer, many of those types of issues.

So there will be a continuing process in this area of having ongoing public meetings to discuss these issues, to get feedback, to

hear from groups, to see what's needed in these areas.

Many of these issues, there's things we've learned in the past, the confidentiality issues are reminiscent of the discrimination issues with HIV testing and screening. And so what we need to do is leverage off the things we've learned in the past, how to do these things.

DR. LANGER: Yes.

DR. DAVIS: It seems to me -- a totally different subject -- that Dr. Jacobson listed a daunting list of issues, and what came across as I listened to the Center directors, each seemed to have picked out one or two issues, primarily more fundamentally science-based to talk about, what seems to be lacking to me, and maybe that wasn't the intent of the presentations, there are some issues that seem to go across all the Centers, and there didn't seem to be a tie together.

For instance, people sort of spoke, one or two mentioned bioterrorism. There's the

whole issue of informatics, microbial resistance, et cetera.

Is that at your level going to be some programs that stretch across these Centers that will tie issues together? Otherwise, you're going to get into redundancies and you'll get people approaching the same problem in different ways, so you won't have a cohesive program. Is that an issue or not?

DR. JACOBSON: Yes. There are actually a number of answers to your question.

It wasn't the intent today to try to tie everything together. We were trying to give sort of an overview of all of the various issues and let people see the different sides that those issues might take.

For issues that cross the Agency, for example, bioterrorism; as Dr. Henney said this morning, we've just instituted an office in the Commissioner's office that is going to do that kind of coordination across the Agency so we have a coordinated effort there.

In some of the other areas, wherever

we have issues that touch every Center, we are trying to do some coordination there. Sometimes it's not as straightforward as it might seem because different Centers operate under different legislative authorities, and so they may have to do things one way as opposed to the way another Center would do it.

But the intent, certainly, is not to have the right hand not knowing what the left hand is doing.

One of the things we wanted to talk about today was which of these issues do you want to hear more about in the future? Because we'd like to pick off a few of them each Board meeting and talk about them, and if you wanted to start, for example, with some of the crosscutting ones, that might be a nice way to proceed.

DR. LANGER: We may want to continue. We will want to continue this discussion, obviously, but along those lines in the 4:00 discussion one of the goals is to figure out what will be in other meetings.

So, actually, that will be very useful to get some thoughts on that.

Yes?

DR. NEREM: Yes, I sort of wanted to pyramid on his comment. When we talk about research, I realize it's very small compared to the program. In the outside world, disciplinary research is the name of the game.

When you think about FDA where you're going to have all kinds of products, therapies, that will be a combination of a device, a biologic device, a drug system; is there actual inter-center research taking place or is each Center doing its own thing?

And that may relate to how do we attract the people?

DR. LANGER: I think this is a good way to get into -- that's a good question -- sort of a good way to get into the slide up there.

It looks like there's several people from FDA that want to comment.

So, yes, if you want to start, and

then Bern wanted to comment, too.

DR. JACOBSON: I think that's exactly one of the issues that we want to talk about and to start dealing with, is this whole interdisciplinary. I mentioned it in the discussion that it raises interesting science questions and interesting regulatory questions.

In terms of ongoing research, right now, I guess, I have to look at the Center Directors; I would say most of it is probably Center driven, but we do have a number of projects, especially in areas that have multiple --

DR. NEREM: Research projects are more or less coordination of activity.

DR. JACOBSON: Well, for example, we have just started a project, a coordination in the microarray area, where we're getting the people together across the Agency who are working in the area to see what should our research program look like in that area; what should we be doing as an Agency rather than having everybody go off and do individual.

DR. DAVIS: Let's just do a fundamental question. I am very familiar with Dan and the group at NCTR, but part of my dilemma is what percent of the Centers you would say are research based.

DR. JACOBSON: It's different for every Center.

DR. DAVIS: That's right. And so I'm trying to get a sense of what percent of the FDA presently would be labeled researchers. It might be different for every Agency, every Center, but there's got to be some FDA; you've got X number of people and a certain percentage of those people where researchers --

DR. JACOBSON: Yes. I don't have that number.

DR. DAVIS: -- in the more stricter sense of this.

DR. JACOBSON: I mean, we could go down the row and we could have each of the Centers tell you what percentage it is, but we can also get you that kind of information.

DR. ANDERS: Can I hop in on this?

Because I think Harold and I see some of the Agency sort of a prism of NCTR where we've both served.

DR. JACOBSON: Yes.

DR. ANDERS: And one thing I know I was impressed with over the years, that the Agency appeared to lack an orderly means of setting priorities for research that would cut across the Centers and to which the -- frankly impressive resources at the NCTR could contribute.

So I understand there's bits of research, there's pieces of research going on in all the Centers.

There's one Center devoted fully to research and not regulation. How do the priorities get set for the Agency?

DR. JACOBSON: Well, I mean -- does anybody want to take a crack at that?

Right now, it's pretty much Center-driven. For example, NCTR, as you said, is essentially 100 percent research.

DR. CASCIANO: About 35 percent of our

research are directly related to chemicals that are nominated by the various Centers for cancer bioassay and risk assessment. So there's quite a bit of coordination between the Centers regarding cancer bioassay.

There's a lot of discussion investigator-to-investigator between the various Centers.

So there's some understanding regarding the kinds of activities that are going on in each of the Centers, and it needs to be better, that's for sure.

But there's a concerted effort now I think where the Center Directors are communicating to a much higher degree in the last year because of constraints on funding and the desire to not duplicate what's going on in various Centers.

I think we're moving in the direction to approach.

DR. JACOBSON: I just also want to give you another number, though, and Janet it is probably even lower than this. But CDRH

research capability of about a thousand people, there are, what, fewer than a hundred that are actually at the bench?

DR. FEIGAL: I think it's about 150 assigned to that group. About a third of their time is not for research (no mic -- inaudible).

DR. JACOBSON: So that's a big difference.

DR. DAVIS: The nature of my question was if you're trying to attract talent, one of the questions, how do we attract people.

You take CBER with Kathy; are we talking about attracting bench-level scientists who do work to go into a group of 20 percent staff, researchers, or are we talking about attracting a single person to come in who understands the scientific arena and be a scientific force but not necessarily do work?

So without knowing percentages, I don't have any idea what kind of people we're talking about attracting.

DR. LANGER: Kathy.

DR. ZOON: Just to address your

question, it actually involves several levels in the Center for Biologics.

We have full-time reviewers, and then we have research reviewers. And I would put the research reviewers in the class of both lab-based and non-laboratory-based research reviewers.

If you look at the level of effort in our Center, we have about 820 FTEs, and probably between -- we have between -- probably it varies from time to time, but probably between 150 to 200 FTEs on research-related regulatory activities. And that would include product testing. That's lab-based activities.

I would be more encompassing and say those are lab-based activities.

So that kind of gives you a feel. When we have research reviewers, they do research and review. The amount of time that a research reviewer will spend on research, used to be in the order of, I would say, 60, 70 percent. That's now in the order of probably

more like 40 to 50 percent.

There's more review responsibilities than there have been in the past so that number will fluctuate based on the regulatory workload of the Center. But their fundamental work in their area of discipline, we use the Staff Fellowship Program, which is -- and the ERDA Program, which are training programs, to bring in new young people into the organization.

The staff Fellows will do research and review. We just modified the ERDA program to allow ERDAs which are post-docs, intramural training program, to do some part of their time of doing review work.

In the past, ERDAs weren't allowed to do any review work. They were only allowed to work in the lab.

So what we're looking at is an opportunity to bring young people in, the best of those young people we'll retain. Those people will turn over and then we'll bring new people in to train. So we use this as sort of a way to look at enhance new science in the

organization by bringing people in from new disciplines that we think they're needed in, and then we try to retain the best.

Now getting more senior people into the organization, which is the other issue is far more challenging. I think it's much more difficult to recruit people into the Agency at a senior level. We've met with challenges in that area and that's a lot more difficult that I think to get really top-notch people from the outside of the Agency, to come in take over these research and review responsibilities.

So I think that's where we need the most help.

DR. LANGER: Bern wanted to make a comment.

DR. SCHWETZ: In response to your question about the number of people, let me give you some ball park estimates of the numbers and some different kinds of jobs.

As we've looked to define how many researchers do we have, how many laboratory workers do we have, how many scientists do we

have in the Agency, we have concluded that it's very difficult to use the personnel classification system to give you information.

Because it doesn't accurately reflect, necessarily, what a person is doing today, because a person might have been hired as a chemist 15 years ago and they're working as a chemist today, but they're still classified as a chemist. So the numbers are not accurate.

But as we've gone through and have tried to reconstruct what we look like, out of our 9,400 people, we estate that between 6,500 and 7,000 is what you would call scientists, scientists being clinicians, engineers, epidemiologists, and the more traditional scientists that you would consider.

So about 6,500, 7,000 of the 9,400 employees that we have.

We estimate that between 2,000 and 2,500 are involved in laboratory work. That's not all research because a lot of that is support work for the field work, support work

within NCTR, within CBER, within CDER.

So these are not people who are doing practical-driven, investigator-initiated research, these are laboratory workers doing routine analytical work, so that's about 2,000 to 2,500 of the 9,400.

Then if you the ask the question, well, how many of these are really doing research of the type that you would say are investigator-initiated, mission-oriented applied research or fundamental or basic, however you want to do it, it's quite a bit less than half of those 2,000, so it's probably closer to a third of those 2,000 people that are actually involved in that kind of research.

But I would also say that we have very, very few people whose job it is to come in and write protocols and do the best science you can. You can count those people on one or two hands.

For the most part, they're brought in to work on a very specific question, so the research may be investigator-initiated, but

it's mission-oriented to a problem that Kathy has with a vaccine or a problem that Dennis has with the method or whatever it is. Does that help?

DR. DAVIS: Um-hum.

DR. SCOLNICK: I guess a related question I have really relates to instrumentation Let me just give you some booked.

If you look at the budget slide that one of you put on, increase in (inaudible) at NIH and industry versus the funding at FDA, it's a rather telling slide, which I'm sure you're all aware of.

You're well aware that everybody says it's kind of a new revolution going on in biology, which is true. The last time we went through a real technological C change in biology was in the late '70s when cloning technology came in, molecular cloning technology came into biology, it really revolutionized biology for the next 10 or 15 years.

That technology was relatively cheap. It was easy to do. Kind of traditional comment that somebody make is you could teach a high school student to do it and they could do it in their garage, if they really wanted to do it after a week's training.

Things that are happening today related to genome sequencing and array technologies which are developing proteonomic technologies which are in their infancy in technology, the high technology machines that are being used, MSMS, LCMS, MS, those are very expensive, hard-to-learn technologies.

And then you add on to that the IT technologies that are needed in order to interpret the data or to begin to interpret the data, and the dearth of people who exist, who can help you develop the algorithms, how in the world, or what is the FDA plan, for trying to get whether you can really do this in house with that kind of budget or whether you're going to have to develop a completely different kind of paradigm to be able to have the

expertise to judge the information that's going to be coming in, maybe not in the next couple years, but certainly over the next 10 to 50 years.

I think that's the most formidable challenge you face. What's your plan for dealing with that?

DR. LANGER: Kathy.

DR. ZOON: Well, I don't have the whole solution --

(Laughter) --

DR. ZOON: -- but I have a tiny piece of it and one that's worth exploring.

I think one of the things I think -- and Dan Casciano and I had this talk a number of times -- to think that FDA will have an entire bioinformatics system that's going to be able to do this all by ourselves and maintain this is out of the question.

So the question is how do you deal and integrate into what's going on at the moment. There's several things that have possibilities.

One is NIH and particularly the NCI has set up this huge bioinformatics program. They're using a contractor, actually, to do it. And so one way, we've met the contractor and we may be able to facilitate our interaction into this, put data into the system, be able to leverage the data, the whole system by feeding into this particular type of contract operation.

And that's not all encompassing but rather than developing our own which would be enormously expensive and probably out of the question, if you can get into a piece of what's already going on and just pay your share of what it is but have access to the whole database, then that's a much more practical application of this.

So those are the kind of opportunities I think we need to look at in the different areas where there's information, and there may be different bioinformatic systems for different types of problems.

DR. LANGER: Yes.

DR. COLWELL: I think it's an opportune time for a lot more interagency cooperation and address the point that you raise.

It seems to me that we need to find a way for perhaps the Center directors or representatives to sit in on panels for some of the areas of funding that we do so that you could see what is coming up and actually be able to be informed and to be able to discuss with those investigators who do get funded, or perhaps if those investigators, one or two, don't get funding, funded, than what would be appropriate for you to pick it up.

So I think this interaction can be very very productive, and I think there are a number of ways we can go about it.

Also, it would seem to me that we could develop workshops that we could co-fund that would address perhaps the microarray chip question. What would be the appropriate way for FDA would limit the resources to be able to

move appropriately and effectively in this direction.

I don't think it in any way would deflect from the basic research mission of the NSF. It would simply be a very nice way to partner.

We do have a program in bioengineering with the Veteran Administration. There we look at esthetic devices and looking at neurological research that our investigators and theirs can collaborate on.

Clearly, no single agency is going to have enough money to do anything completely.

Obviously, at least to me, collaborations are critical.

You're gong to have a heck of a time getting information technology expertise. Every agency has been reading about it in the newspapers. We don't pay competitively, but there's some attempt to try to step out of the box on that, and it may happen. But in the meantime, it seems to me that again we ought to be able to team up in a way that we could

provide perhaps expertise that we jointly contract out or work on obtaining.

We don't try to maintain our in-house computer systems. We do that by contract. But there may be some way of being able to carry that out.

In any case, I think there's some very good opportunities to enhance the research capability of the FDA by this kind of partnership and a more effective, maybe a tripartite partnership with the NIH in the basic research areas that are keen interest and great importance for the FDA.

DR. SCHWETZ: Rita, we would very much like to engage in those discussions with you to figure out how we can bring these two parallel organizations together with bridges.

DR. COLWELL: Let's do that. We'll follow-up on that.

DR. SCHWETZ: We'd like to do that.

DR. COLWELL: Yes.

DR. LANGER: Yes?

DR. ROSENBERG: In terms of tapping

expertise as you have on the slide, that would also help solve that problem because I think one of the places you could very nicely attract from is the NIH, and I don't think you partner well with them at all. I don't think they know you exist.

In fact, the industry knows you exist far more than the NIH knows that you exist, and yet given the structure and how you do business the NIH scientist would want to move to this kind of a field and this kind of analysis, this would be a much more attractive switch for the NIH-type scientist. And I think you're missing out on that opportunity by not doing more of this as well.

DR. LANGER: Mike.

DR. DOYLE: Following up on what Rita said, I think she's right on, but there are bigger opportunities than just NSF and NIH. I mean, DoD is also considering getting into the microarray area and tremendous amounts of dollars will probably be invested into that in terms of infectious diseases and all, and I

could just see an excellent partnership there with FDA and USDA and those interested in food safety.

DR. DAVIS: Further goes to my question about the organization of programs and processes across the agencies. And it speaks of even outside of the Agency, because these are going to be such daunting issues that the costs and the amount of material to be regulated or controlled is just tremendous.

As Ed was mentioning, the kind of thing, the data that we're going to be generating with microarrays and who's going to have the resources to generate all that, I firmly believe if the FDA thinks they have trouble now with clinical data and all that stuff that's just sitting there, that it would be wonderful if somebody could go through it and make heads or tails out of it.

It's going to get even worse with the amount of data that we're going to be generating in the future.

FEMALE VOICE: Yes, I agree.

DR. DAVIS: You won't have a place to store it all.

And so I think it's imperative that there be some cross-center, cross-agency initiative, and I wouldn't leave industry out, especially for those of us who are regulating. I think perhaps trying to get in early to help drive where we're going and how we're going to be regulated and getting some agreement on what processes ought to say and what data we ought to submit, how that data ought to come in, et cetera.

So you might be able to get some partnership there with resources and expertise.

DR. LANGER: Bob and then Rita.

DR. NEREM: Yes. Two comments, first picking up on Rita's comment.

NSF has engineering research centers, has science and technology centers. Some of those centers are operated in areas very pertinent to FDA so that's another place to partner.

Beyond that, I want to ask Liz a

question.

Do you have in your new position a budget for crosscutting science initiatives or is all the research money out there in the Centers as part of their -- whatever they get from Congress? I don't know how this works.

DR. JACOBSON: I have requested a small budget for sort of seed projects, seed money, to get cross-agency things going, but no, I don't have a budget.

DR. NEREM: Never request a small amount. You should always request a large amount.

(Laughter)

DR. JACOBSON: At FDA, we only have small budgets.

DR. LANGER: Bob will be a special consultant. He knows how to ask for a lot of money.

DR. NEREM: And get it.

(Laughter)

DR. LANGER: Rita.

DR. COLWELL: Actually, there is an

interagency initiative on information technology.

I want to pick up on Mike's comments about a lot of money put into it. Indeed, there is. And again the comment about the across the agency, even that initiative within the NSF is an agency-wide initiative because it involves every single aspect of it.

Building databases and research on building databases and searching databases is worth putting a lot of money into in DARPA, particularly putting a lot of money into it.

Now this is a political issue, but it seems to me that the FDA ought to find a way to get into the interagency information technology initiative. Serving the FY 2001 budget is closed, but the FY 2002 is in the preparation and your appropriate political contacts. I don't know what they are but, in any case, I think an argument can be made for new money or database building and searching and for software development that can be done collaboratively as part of the interagency

initiative.

DR. NESTLE: I don't know about anybody else, but I'm just enormously alarmed by this morning's discussion.

We've heard three things at this meeting that put together, have me in a complete panic about this.

One is the budgetary situation.

The second is the Agency's budget is determined by the Agriculture Committee not by a committee that deals with health.

And the third is the collection of demands on the agency that we've heard about this morning. This is obviously a crisis situation and the kinds of suggestions that are being made are band-aids dealing with a situation that seems to me is overwhelmingly alarming.

I'm a consumer representative on this Committee and, as such, I get to say outrageous things like this --

(Laughter)

-- but I think this is a national

crisis.

That's how I see it from what I've heard this morning.

We have a situation in which all of these new technologies and new devices and new drugs and new everything are coming on the market with absolutely no ability to determine whether they're safe or not for the public.

Something has to be done about this and I think it's great to talk about interagency cooperation but I think it's going to take a great deal more than that, and we ought to be talking about it if we can.

DR. COLWELL: Yes. There's no question. I don't think anybody around the table is going to argue about the budget not being sufficient for FDA, otherwise, we wouldn't be here. But we have to face the political reality.

I don't think the interagency collaboration is a band-aid. I think having been involved in various panels and committees and things for FDA over the last 15 years, it's

very clear that a major infusion of money from Congress is not on the horizon.

It isn't on the horizon, really, for any one agency, but I think we have to find innovative ways to address just the issues that you're raising, the budget shortfalls, this burgeoning of science and technology that's occurring.

It's changing. That is somehow changing the whole pharmaceutical approach to human health. It's turning into a very much complicated kind of thing. It's nutraceuticals, pharmaceuticals, it's preventive medicine in a different way, which means engaging the public and the consumer in a much more informed way, which means that probably the FDA is going to have to develop a really good web site for information for the consumer. That's another step to take.

So there isn't any simple solution. But we can't just wring our hands. We've got to find ways to help out.

DR. NESTLE: Don't get me wrong, I'm

not opposed to interagency collaboration, I just wouldn't underestimate its difficulty.

DR. COLWELL: Oh, I agree with you.

DR. DAVIS: I'd also like to say I share your alarm; however, I wouldn't want to sit here quietly and say I feel that the drugs that are coming out on the market, that we have no way of attesting to their safety, et cetera.

As a representative of a company who provides drugs to the public, I feel very comfortable that what we do allows us to be somewhat comfortable with the drugs that we're putting on. I think FDA does a great job in that.

So I am not -- I don't share your concern that we have no way of attesting for the safety of the products we're putting on the market.

I am alarmed that the task that is before us with incorporating science as it is developing is a daunting one, and we better do something tremendous with or dramatic to fix that problem; but I don't go to sleep at night

concerned that we're putting unsafe drugs on the market.

DR. LANGER: Other comments?

It sounds like there are a few.

Bob and then Liz.

DR. BUCHANAN: As you wrestle with coming up with recommendations, I do offer a note of caution, having been in an involvement the last three years in a very large interagency type of activity.

The reality of budgetary increases, which we all like to get, is that they tend to be small, and more often you're slated to do something which means that you have to stop something else.

So, really, what we're looking for often is advice on budget optimization not just relying on budgetary increases. So one of the things that we have to wrestle with is if we're going into genomics or proteonomics or all of the other new technologies, what in our mission are we going to stop doing; for example, do we quit looking in the food field, warehouses?

That's an issue.

How often do we get to go in and inspect a warehouse, because in most situations it's a zero sum gain.

If you put more money into the foods program, who are you going to take it away from? Again, that's the issues that we've been wrestling.

So as you think of recommendations, think also of the impact those recommendations are going to have if we don't get budgetary increases.

DR. LANGER: Liz.

DR. JACOBSON: I just wanted to say that with respect to the things that you said, Dr. Nestle, I'd like to think of it in terms of urgency.

The whole point of going through this kind of a description of what we're facing is to bring out and make more public, make more obvious what are the problems that FDA is facing, and I think one of the things that

interagency collaborations can do for us is to help get our problems on other people's agenda.

It's really difficult, though. I agree with you. And our priorities, our mission, isn't necessarily the other Agency's mission, and so it's difficult to get attention, but we kind of have to deal the hand that we're dealt, and right now we have a lot of incredibly pressing technologies and products that are coming at us.

I also disagree with what you said, that you know we don't have any way to know that anything is safe. I think we would all disagree with that.

We also have to sit and sort of try to strategically think, how are we going to change the way we're doing business because I think we are sort of in a paradigm shift. We can't keep doing things according to the old paradigm. That simply isn't going to work.

Meetings like this one, one of the things we're hoping to get is some discussion and some advice on directions that we should be

moving and, frankly, ideas for ways to move out.

DR. SCOLNICK: I would ask you back a question, and it's a tough question.

Do you have a strategic planning process in place within the agency to try to address the kinds of questions that the Board is asking you about this morning?

If you do, you know, are you in a position in some period of time to come back to the Science Board with an overview of that plan as to how the Agency is planning to spend its money and change how its doing, whatever it's doing. Or if you don't have that process in place, what would it take to put it in place? A really good strategic plan for the FDA in the new millennium?

DR. LANGER: Do you want to answer it and then Janet has a comment.

DR. SCHWETZ: Jeff Weber, the head of our Budget Management Office, may like to comment more on this, but one of the things we've been trying to turn around in the last

few years is to move away from the budget determining what you do to us determining what the budget needs to be for the things we need to do.

There's been a lot more attention paid to that in the last few years than there were in the previous years that I've been in the agency, so we're trying to get that turned around through the large number of meetings that we have to talk about priorities and needs and what can we not do if we're going to change priorities before the budget numbers are sorted out.

So we've been going through that process pretty religiously in the last few years to get people to share ideas early on about what the priorities are to be able to integrate them between and across the Centers and the rest of the Agency.

So there's big progress in that area. But even when we come up with a budget and the pieces get lopped off a lot of that planning comes to no avail when the budget isn't near as

big as what we thought it needed to be.

DR. LANGER: Jeff.

JEFF: Right. I've been here for one full budget cycle now and the tail end of the last budget cycle, and what I see in the beginning of the cycle what we are trying to do is some strategic planning, although it's short-term strategic planning as opposed to long-term strategic planning.

And what myself and the head of the planning office have done recently is gone around and met with each one of the Center directors and each one of the deputies to try and design an approved process for future years.

And one of the continuing themes that keep coming out is that we do need to do some type of long-range strategic planning, and eventually we're going to come to the leadership team and make a recommendation on a revised process based on everything that we've heard from the Center directors.

There is long-term strategic planning

in each one of the Centers now, or most of the Centers, are either have a strategic plan or on the verge of completing a strategic plan, so it's probably a good idea for the Center to get into some long-range strategic planning as well.

I also want to touch on the point that Dr. Schwetz made. We can have all the strategic planning and all the budgeting up front in advance, but when we start with a budget that we submit to the Department it gets whittled down, it goes to OMB, then it goes to Congress.

When we finally get our budget back, we're lucky to get enough resources to continue to pay the salaries of our employees, because we have not been getting our current services paid for so we have to absorb a 3.7 percent pay raise this year, plus within grades and promotions if you want to keep your good employees, awards, et cetera, otherwise, the attrition will be even greater than it is now. And that's about $42 million.

So that right off the top whatever Congress gives us this year, we're spending $42 million to maintain our existing staff.

So there really isn't much left to try and shuffle around between priorities even if they don't give you sufficient resources.

And I'll give you one perfect example.

Congress decided this year that antimicrobial resistance was a very high priority for them. We have resources requested in our budget, six or seven million dollars, but they added $3 million on top of that for CVM, well needed, we'll put it to good use.

However, in doing that, they decided they're just going to take the $3 million away from CBER. So CBER now has less money for blood work, less money for vaccine work, less money for tissue work, without any consultation with FDA as to how do we want to re-prioritize those resources.

So we can prioritize all we want, but when those decisions are made without our consultation, it's very difficult.

We've had conversations internally, where do we want to shift resources if CBER needs help because they have to do that work as well.

And everybody is so strapped that there really is no other place to take the money from to providing that additional support to CBER.

So those are the kind of issues that we're dealing with. I mean, it sounds simple on the surface but it is very difficult to juggle the dollars when you don't really have enough to do your basic mission to begin with.

DR. LANGER: Janet, do you want to make a comment?

DR. WOODCOCK: Yes. I just wanted to provide a couple points of clarification with respect to what Dr. Nestle said.

As far as drugs, we probably, right now, given the science have the greatest predictive ability ever for humans to predict drug safety post-marketing, but it isn't ideal and we're still not where we should be. So it

isn't that we can't predict drugs toxicity profile after marketing, it's just we aren't at the level.

Society, I think, is required, demanding a higher level of assurance and confidence than they have in the past and we need to keep pushing our ability to do that.

With respect to what Dr. Davis asked, CDER, I think my calculations are correct, 3 percent of our employees are engaged in laboratory research. It's a very small number of people. I would say they are fully-leveraged right now.

So given our budgetary constraints, it's very difficult for us to do any more cross-collaborations than we are doing.

For example, with spectroscopy, we use St. Louis University and other partners that we have to give us access to advance techniques. That's probably the only way we can do it with just a handful of people.

So our ability, actually, to leverage further with further cross-organization

collaborations is fairly limited, simply by the number of people we have.

DR. LANGER: Other comments?

(No response.)

Why don't we take a break. We'll get back together at 1:00 for a couple of comments.

(Luncheon recess.)

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

(1:08 p.m.)

DR. LANGER: We're going to start now with Public Comments, and we have Doris Haire, from the American Foundation for Maternal and Child Health would like to make some comments.

Open Public Comment

MS. HAIRE: Good afternoon. I appreciate this opportunity to share my concerns with the members of the FDA Science Board and to ask the Board to urge the FDA to create an Interdisciplinary Obstetric Advisory Board comprised of pediatricians, pediatric neurologists, behavioral scientists, midwives, obstetric nurses, and obstetricians to evaluate the safety of drugs to be administered to pregnant and parturient women.

The FDA cannot expect a Maternal Health Drug Advisory Committee made up almost exclusively of obstetricians to be objective about the drugs they have administered to their patients.

Such a group does not have the

training or expertise to determine the delayed, long-term effects of the drugs they administer to parturients or on the long-term development of the exposed offspring.

I've heard obstetricians in that Committee remind the group that there would be serious repercussions for obstetricians if the Committee were to recommend that a drug previously approved by the committee to be removed from the market.

The fact that the makers of Pitocin, Marcaine, Sublimaze, and other drugs commonly used in obstetric care have chosen to remove their labels from the Physicians Desk Reference, only adds to our conviction that they wish to withhold ready information regarding the risk of their products not only from the public but from the doctors and other health care providers.

Most nurses and midwives that I have discussed this with tell me that when they have asked the hospital pharmacist for a copy of the package insert they are refused.

I am concerned that as the number of children with learning disability, autism, dyslexia, attention deficit disorder and hyperactivity continue to mount to a frightening number, the FDA does not appear to make a strong endeavor to see if obstetric drugs contribute to these problems.

For some reason, the scientists seem to have let the science of human parturition slip through the cracks. As evidence of this scientific vacuum, a recent *Report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century* failed to mention the need to improve the safety of childbirth for the woman and her baby and the potential adverse effects of obstetric drugs and interventions on the neurologic development of the offspring.

In light of the soaring rate of autism, 500 percent in 10 years in some states, it behooves the FDA to question whether cervical wideners, uterine stimulants and various pain-relieving drugs administered to the parturient permanently alter the brain

circuitry of the fetus and newborn sufficiently to interfere with the normal dendritic arborization within the infant's brain.

Virtually all drugs administered to the parturient cross the placenta, enter the circulatory system and brain of the fetus and newborn infant where the drugs and their metabolites may remain for days if not weeks.

It is ironic that women who do not wish to become pregnant are provided a package insert with their contraceptive drugs to ensure that they understand the risk of taking the drug. Yet the woman who wishes to have a safe birth and experience for her baby as well as herself receives no package insert advising her of the known and potential risk to her and her baby.

I urge the Science Board to recommend that the FDA require package inserts to be made available on request to all expectant mothers who wish to know about the drugs they will be offered during pregnancy, labor, delivery, and postpartum.

Consider the information the doctor receives regarding the risk of oxytocin. The manufacturer of oxytocin warns the provider in the package insert: "Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, fetal deaths, and permanent central nervous system or brain damage of the infant due to various causes have been reported to be associated with the use of parental oxytocic drugs for induction of labor or for the augmentation in the first and second stages of labor."

In addition to the more benign effects of uterine stimulants, the American manufacturer of Pitocin points out in the package insert that oxytocin can cause maternal hypertensive episodes, subarachnoid hemorrhage, anaphylactic reaction, postpartum hemorrhage, cardiac arrhythmias, fatal afibrinogenemia, premature ventricular contractions, pelvic hematoma, uterine hypertonicity, uterine spasm, tetanic contractions, uterine rupture, increased blood loss, convulsions, coma, and

fatal oxytocin-induced water intoxication.

Yet, I don't hesitate to say that none of the women, or virtually none of the women in this country have any idea of the risks of oxytocin.

The following adverse effects of maternally administered oxytocin have been reported for the infant and the fetus -- bradycardia, premature ventricular contractions, and other arrhythmias, low one-minute and five-minute Apgar scores, neonatal jaundice, neonatal retinal hemorrhage, permanent central nervous system damage or brain damage, and fetal death.

Uterine stimulants which foreshorten the oxygen-replenishing intervals between contractions by making the contractions too long, too strong, and perhaps even more important, too close together increase the likelihood that fetal brain cells will die.

All of these effects increase the possibility of neurologic insult to the fetus. No one really knows how often these adverse

effects occur because, as you know, there is no law or regulation in any country which requires the doctor to report an adverse drug reaction to the country's drug regulating agency even if the patient dies.

I don't know how many of you saw yesterday's *Los Angeles Times*, but I was very pleased that they included that in the information on the front page.

There are growing indications that oxytocin may contribute to the incidence of autism. As I said, a 500 percent increase in 10 years in some of the states.

But is oxytocin or is it the drug used in epidurals that then precipitates the need for oxytocin?

Considering the following information which the U.S. Food and Drug Administration currently requires the manufacturer of bupivacaine, the drug most commonly used in epidurals. The government-approved labeling for bupivacaine, which is produced by Marcaine, reads:

"Local anesthetics rapidly cross the placenta and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity. Adverse reactions in the parturient fetus and neonate involve alterations in the central nervous system, peripheral vascular tone, and cardiac function."

But this is even more interesting:

"Neurological effects following epidural or caudal anesthesia may include spinal block of varying magnitude --including high or total spinal block-- hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia; paresthesia; weakness; paralysis of the lower extremities and loss of sphincter control, all of which may have slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; and cranial nerve palsies due to traction on

nerves and the loss of cerebral spinal fluid."

"Neurologic effects following other procedures or roots of administration may include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery."

I'm here because I have tried to do all the proper things first, and my husband always, being a lawyer, always says, "Do the proper things first, and when that doesn't work, try something else." So that I hope that the Science Board of the FDA will encourage the FDA to move to require package inserts for all obstetric-related drugs.

Rosenblatt and her fellow investigators found the bupivacaine administered to the mother during labor can have a prolonged effect on the subsequent development of the exposed offspring. The investigators found that newborn infants, when greater exposure to bupivacaine in utero were more likely to be cyanotic and nonresponsive. They also found that visual skills and

alertness decreased significantly with increases in the cord blood concentrations of bupivacaine, particularly in the first day of life, but also throughout the next six weeks.

Adverse effects of bupivacaine levels on the infant's motor organization, his ability to control his own state of consciousness, and his physiologic response to stress were also observed.

Sepkowski and Barry Braselton carried out a similar investigation after that, and they found all of their data supported the findings of Rosenblatt.

As early as 1975, the FDA acknowledged in its *General Considerations for the Clinical Evaluation of Drugs in Infants and Children* that drugs trapped in the infant's brain at birth have the potential to adversely affect the rapidly developing nerve circuitry of the brain and central nervous system by altering the rate at which the nerve cells in the brain mature; the process by which the brain cells develop individual characteristics and capacity

to carry out specific functions; the process by which the brain cells are guided into the proper place within the brain and central nervous system; the interconnection of the branch-like nerve fibers as the circuitry of the brain is formed; and the forming of the insulating sheath of myelin as a fat-like substance around the nerve fibers which help to assure the nerve impulses -- the messages to and from the brain -- will travel their normal routes in their normal rate of speed.

Now the work of Zheng, Heintz, and Hatten reaffirm that the migration of neurons among the glial fibers within the brain can be altered by changing the normal chemistry of the rapidly-developing brain.

At no other time in an individual's life is his or her brain more vulnerable to alteration, trauma and permanent injury during the hours which surround that individual's life.

And, yet, the FDA it seems has completely disregarded the potential of these

drugs to affect the baby, and I hope that -- I have much more that I would like to say but I realize that my time is up -- but I hope that the Board of Science -- there doesn't seem to be any other source that we can turn to at the FDA -- but I hope that the Board of Science will see to it that the FDA begins to look at the effect of obstetric-related drugs on the well-being of the infant.

We all have an investment in these children, and I doubt whether there's anyone in this room that doesn't know some child who is learning disabled or autistic, and there is a good chance that we can prevent this.

Thank you.

DR. LANGER: Are there any comments?

(No response.)

Thank you very much.

MS. HAIRE: You're welcome.

DR. LANGER: We'll make sure that this gets to the appropriate places.

Are there any other public comments that anyone wants to make?

(No response.)

It looks like there are not. Why don't we continue with the agenda and have David talk about the programmatic peer review for the Center of Devices and Radiologic Health.

DR. JACOBSON: While David's getting set up, let me just make a comment here.

CDRH is the next Center at FDA that's going to undergo a peer review process, and David's going to talk to you about that. CFSAN, CBER, and NCTR have already done a peer review process, and at the last meeting we talked about the results of the CFSAN process, and after that meeting Drs. Fennema and Schwetz put together some guidelines to be used for the peer review process, and I just wanted to tell you two things:

(1) The guidelines are in your notebooks so you can see what they look like; and,

(2) Don't surprised that the presentation you're going to hear right now is

not following all of the guidelines because CDRH was already underway as those were being put together, and we sort of see that process as a transition, and we didn't want to delay their effort by holding them up.

David.

DR. FEIGAL: Thanks very much.

Programmatic Peer Review - CDRH

DR. FEIGAL: What I'd like to do today is present to you work that's been in progress. When I came to the Center a year and a half ago, one of the first things I did was ask the senior leadership to begin a process of evaluating how we use science in the Center.

I was in the Center for Biologics at the time of the external review, and I was actually eager to have our Center participate in the review and talk to Bern Schwetz about the possibility that we be up next.

And we're in a process here where we have formulated a fairly mature proposal, but it's not cast in stone. We can modify it, we look for your suggestions about how to make

this more useful. I think you'll see we have incorporated some of the suggestions that have come up from the time of the other reviews.

I wanted to actually begin this by providing a little bit of background about the Center and a little bit of background about another process which has been going on at the same time, which is a strategic review.

An appropriate place to start in talking about the Center is to talk about our mission. It's actually a mission that's very close to the heart of the employees in the Center. CDRH promotes and protects the health of the public by insuring the safety and effectiveness of medical devices and the safety of radiological products.

It's a very broad mandate. It includes thousands of types of products, both therapeutic products and consumer products in the case of radiological products.

The consumer protection, our sort of modus operandis is similar to other therapeutic products. One large category of consumer

protections and where we apply our science is in the area of risk management.

As in the case for drugs and biologics, there are devices that require clearance before first human use in the form of an investigational device exemption.

We of course are concerned about the safe experimental use during product development and of the evidence needed to be sure that the risk of widespread use that occurs with market approval are warranted and in the post-marketing period we had programs that evaluate the adverse experiences.

The other -- and I think probably the crosscutting, and I'll make this case a little bit later -- is that the really fundamental underpinning of the way that we do business is as a science based, regulatory decision body.

The majority of that historically has been evidence based. But then as I mentioned this morning, increasingly, we're utilizing standards.

Then, finally, there's part of the

operation that has to do more with the assurance of the integrity of products, the enforcement sides of dealing with fraudulent products, products which are poorly manufactured, or inappropriate and bad clinical practices.

The Center for Devices, actually looking around the posters around the room, Center for Drugs forgot that FDA stands for the Federal Device Administration. They left off the 1976 Device Amendments.

(Slide.)

Before 1976, devices that were regulated were regulated as drugs, with new drug applications.

But in '76, device amendments were passed which defined devices, gave us authorities to move against violative products, established a tiered system of control based on risk, and established standards of evidence for marketing claims.

I think you really have to sort of understand a little bit of the background of

the system to understand what the scientific task is we deal with.

In 1976, there were probably as many as 100,000 medical devices already on the market, and these are sometimes referred to as pre-amendment marketed devices. And there was a process of classifying them by risk, from the highest classification, Class 3, down to the Class 2 and Class 1.

And there was a process for bringing products onto the market by establishing that they were substantially equivalent to a previously-marketed device.

All devices have certain types of controls. There are general controls that include facility, registration, and product listing;

Premarket notification except for the majority of the Class 1 devices which are exempt;

A requirement to follow good manufacturing practices or quality systems; and,

A system for reporting device failures.

(Slide.)

The intermediate risk classes are the first area we actually begin requiring information that's specific to the device. If you look at the Class 1 devices, the controls there are very broad and general controls and do not relate to the performance of the specific device.

So the largest category of devices that are on the market and that are approved today are based on establishing that they are substantially equivalent to a predicate, to a product that was marketed before 1976, and when a product is cleared it joins that group of predicates.

(Slide.)

To give you an idea of the size of this, these are the number of applications over the last 20 years.

These are the number of premarket notifications of 510(k) applications, and if

you work this out to a roughly 200-day business day, it means that day in/day out there are about 20 510(k) approvals or clearances per day by the Center.

This is the typical application, or about 40 hours, if you take the average number of hours, the number of FTEs working in this program, to evaluate this group of products.

Then in addition to these four to five thousand number of new devices that come into the market every year, there are an approximate equal number of devices which are exempt.

One of our basic challenges is how do we work within this framework and how do we provide consumer protection and science-based regulation for this group of products.

The other group of products, and probably one that you will see more and be highlighted more in terms of the review because the more novel ones are more of a challenge to us, scientifically, are the products which require premarket applications, the Class 3 products.

And when there's not substantial equivalence to a predicate then you must establish that the product is safe and effective.

This is the volume of the PMAs, and the thing to note on this is that the scale is one log smaller. The other scale went up to about 9,000, this scale goes up to about 900.

(Slide.)

The blue line at the bottom is the number of new PMAs approved per year, and it's actually about the same volume as the number of new molecular entity drugs. It runs between 60 to about 100 per year.

The red line are the supplements to those PMAs, and they have a structure that's very similar to a drug supplement. If there's a new indication or some other significant modification that requires a supplemental application.

Then the green bar are the actual number of IDEs. These are equivalent to INDs, if you're more familiar to the drug process,

and it actually shows you the relatively small volume of products that actually are required to have FDA supervision for the clinical studies.

In fact, one of the things that shapes the scientific challenges for the Center is that of devices that come to the market, fully 90 percent of them will not have human testing, and quite appropriately so.

So we need to take a look at what it is that we need to evaluate these family of devices.

When we think of the organization of the programs and of the resources, it's often phrased in terms of a premarket program and a postmarket program. In fact, I think we used those words this morning.

And the consumer protections are sometimes grouped under that. If you look at the premarket consumer protection controls, we think of the requirements for safe experimentation, premarket safety, the standards to establish effectiveness before a

product is marketed, the process of inspecting research and IRBs.

On the postmarket side, there are all of the laws, actually some of the oldest authorities that the agency has, about truthful promotion, systems for adverse event reporting, postmarket studies, and manufacturing inspections.

Now, as we thought a little bit about the paradigm for reviewing the science, one logical way is to, and I think there's an element in some of the past reviews, is to think of this basic system, to think of our laboratory and our research programs, and then have the science review come in and take a look at that.

(Slide.)

If you look at where we've actually got our resources deployed, though, and you can take a look at primarily fiscal year '98, if you look at '95, it's similar, although you'll see a shifting of all areas into the premarket program.

But you'll see if we actually just showed you the programs that were strictly doing research projects and science and laboratory projects and epidemiology and some of the other areas, that we would actually only be showing you less than 10 percent of the activities of the Center.

As a science based and an evidence based regulatory agency, we sort of asked ourselves, is there another way to better share the vision of how we see ourselves as a science-based organization.

So instead of premarket/post-market, we took a step back, because these are awfully regulatory terms and an inventor doesn't say, "Gee, I'd like to have a premarket device or a premarket invention or a post-market inventions," we thought a little bit of the whole process of the life cycle of a device.

Device begins as a concept. Prototypes are built. Preclinical work, if it's needed, is done. A clinical program is begun. Again, this won't be needed for every

type of device, but this information is compiled together to begin scale-up for full commercial manufacturing and commercial marketing.

There's a period of commercial use for the product, and then there's a period where the product is obsolete and it's replaced by another product. It may gracefully fade from the market or it may be withdrawn or it may more dramatically be given the hook but that's usually not the case.

So, in fact, if we think about in a non-regulatory sense the entities we're dealing with we're really dealing with a product lifecycle, and it's a product lifecycle that it's intensely interconnected.

One of the difficulties of trying to do these things separately is what you learn from the preclinical phases or from the prototype informs the way you design your clinical program or has an impact on your manufacturing experiences.

(Slide.)

Similarly, manufacturing experiences are going to feed back to the choices you may make about the way that you're going to prototype the next generation of the device so that, in fact, even this kind of an interconnected diagram of product development really reflects for devices a more complex process, which is that of a pipeline.

One of the things that's different about devices than drugs is that the agency has no authority to grant any type of patent extension or exclusivity, not even orphan drug exclusivity.

The one mechanism we have, Humanitarian Device Exemption, is actually much more like a treatment IND, and it does not grant any marketing exclusivity.

The average life expectancy -- or not life expectancy -- average time on the market for many devices is about 15 to 18 months, and in fact, there's some types of devices that are replaced by another version about every six months. If you've ever tried to versions of a

PC, two copies of a PC about four months apart, it's a little disconcerting to have that brand new PC you bought no longer manufactured, but the device manufacturing world is very very much like that.

As we thought about this process and thought about how different that was than the drug process where if you're lucky with a drug you get it marketed early in its patent life and you'll have a prolonged period where you can do post-marketing studies.

It's almost irrelevant in some ways to talk about post-marketing studies for devices because the product will be off the market and replaced by the next generation before you can really launch those products.

And so that as we began looking at this and saying to ourselves what is it about devices and device regulation that we need to make different it was that we need to think about all the connections and we need to think of them as a family of products across multiple generations.

Part of this actually came from a comment about in vitro diagnostics for an infectious disease screening agent where someone from the Center for Disease Control said, you know, you only get over other version of this product.

In Europe, they market -- every time they update it and make it a little more accurate, it goes on the market, but your regulatory cycle is too long and there isn't time to get them on the market so they actually give you every other version of that. And that didn't strike me as something that fit well with our public health mission of promoting rapid access to product improvements and product corrections.

Where does scientific work come from? This is another way of sort of organizing and sort of saying, what are we trying to get ready for as we look for an external review of our science.

Some of the work is very product specific; so, for example, if you take the