

consider clinical experimentation which is not carefully regulated, I get the jitters. But this is strictly a personal problem and it's not meant to convince anybody else about the point of view that I have.

And there are more cases that were discussed in the August 6, 2001 Newsweek issue on page 36-42, thanks to my wife pointing it out to me. These are the reasons that I would like to propose here that possibly enhancing the role of regulatory science, animal research, might result in minimizing these types of fatalities.

Before I become more specific, I would like to first refer to the FDA 2001 Science Forum that was concerned with establishing linkages between various scientific disciplines. On the sideline, I would like to say I am very much interested in this whole question of linkages, and it is my opinion that a meta search engine that links different type of data banks with their keywords is essential for us to move into the 21st century and not feel inundated with information.

Okay, excuse me. I believe that there is another opportunity to establish new linkages between animal and human research, and by doing this possibly increasing safety of volunteers in clinical trials. That is one thing that I noticed, I am very much clinically oriented in terms of a biomedical engineer, and one thing I noticed when I joined the IACUC committee is that that linkage was really not there, at least the way I saw it. I did not notice any linkage. People did their animal research but they didn't realize that it has some links with human research. Again, this is my personal point of view.

Based on my own research, I have gotten involved in discussion of global-local thinking and the information explosion, so I really felt pretty good. Sometimes when you go on your own, you feel that you are really kind of crazy. I still am probably kind of crazy, but at least here was an instance where I was not.

Enhancement considerations. Since I do not have specific data available pertaining to

results in regulatory science animal research, all I can do is ask a few intuitive questions and then hope that the Board will have time to respond to them, and I'll be covering three topics: IRBs, FDA reviews, and in-house animal research.

Institutional Research Boards. Could the Institutional Research Boards enhance their awareness of considering animal research in terms of trying to minimize fatalities in clinical trials? And as I was re-reading this paper here, what came to my mind, maybe my immediate training in this respect might be purposeful.

Number two, FDA reviews. Could the awareness of FDA reviewers be enhanced in terms of assessing whether animal research is needed before human trials are approved? Since I worked in FDA until 1995, I realize that the FDA reviewers are under terrific pressure to get things done, so this is here kind of a rhetorical question. It seems to me that if this were done at all, then some more money must become available to project for this particular purpose.

In-house animal research. Could the FDA focus on doing animal research in support of clinical trials be enhanced. Now, that I think is something that you can subconsciously develop, because you can always have ideas at night where you don't get paid for them and bring them in in the morning. But it seems to me that if this is in the background of animal researchers, this idea that yes, that thing of those clinical trials, that kind of self-consciously it seems to me eventually they would go in that direction, but again this might mean some training.

Final comments. In support of my proposal of enhancing regulatory science animal research, I would like to refer to the statement of Dr. Schwetz in his introduction to the 2001 Forum: "As we continue to enhance the science foundation of FDA, the effective training and retraining of our scientific and our medical personnel is among our highest priorities."

And this really brings out not only the training at FDA which I greatly enjoyed while I was

there, but also the outside world like hospitals and so forth. Can there be maybe a foundation that has too much money, could spend, could start a grant in this direction?

Accordingly, it might be useful--I kind of interrupted this, but based on the last Forum and the statement of Dr. Schwetz--it might be useful to have a session on enhancing regulatory science animal research at the 2002 FDA Science Forum, if possible, or instead later on at the 2003 Forum.

I like to thank the committee for giving me the opportunity to present my very, very, very personal views. Thank you very much.

CHAIRMAN LANGER: Thank you. Any comments, questions? Thank you very much.

The next person to speak is Scott Ratzan, who is the editor of the Journal of Health Communication.

DR. RATZAN: Good afternoon. Thank you, Mr. Chairman, committee, and everyone here for the opportunity to speak today.

I wanted to sort of switch the discussion,

which I think presages what Dr. Nerem is going to talk about in terms of some of the challenges subsequent to the public comment period on the need of how we communicate risk and how we make regulatory decisions, and the impact that it has upon the public.

As you can see, I edit a journal, the peer review Journal of Health Communication, and I'm on the faculty at three different universities where I basically teach health communication, one in the School of Epidemiology and Public Health at Yale; at Tufts in the Department of Family Medicine and Community Health; and at George Washington in Public Health and Health Services.

As I'm told here, I'm supposed to also disclose other conflicts. I consult on a variety of areas, with the common denominator being communication. I consult with about five different pharmaceutical companies, on and off, dealing with communication issues. I'm on the study section for the Agency for Health Care Research and Quality, for communication. I consult with about six other

Federal Agencies, NIH, CDC. I've done consultations with WHO and a variety of others. I also have sat on two IOM committees, most recently in terms of communication with quality issues and health indicators for the country.

With all that being said, nonetheless I'm representing myself today. I'm not representing any of these other groups that I've spoken about. And I'm trying to raise the debate to deal with ethical communication.

There were busy Brueghels in the 15th, 16th century. Our life is just as complicated today. However, we try to explain a lot of things in two dimensions. We try to explain things with one versus the other.

So what I'm going to try to do is a 10-minute challenge for me, as Celeste had given me. Background on communication. Lessons that we have learned from BSE. Thimerosal and vaccine risk. And recent challenges that are very fresh in our mind, dealing with anthrax. And some ideas that I think this committee could well consider and

advance the public health.

Our goal is really similar to what the World Health Organization has presaged many years ago: "Informed opinion and active cooperation on the part of the public are of utmost importance in the improvement of the health of the people." Clearly we embody that in the open process, and again, thanks for even speaking today.

But how do many of us make decisions, whether we're on advisory committees, different committees, and so forth. Sometimes we say the data speak for themselves. Of course we know, we've already heard data don't speak. There is data, information, knowledge, and wisdom. We can explain the issue with statistical significance. Can science always explain the areas? We have progress that is incremental with evidence-based hypothesis testing, the 21st century approach. And we still believe that scientific method can solve most dilemmas.

But how does the public make decisions? Very differently. Many think the mouse is a little

human, or even worse, the plural form of the word "anecdote" is evidence. And this goes back to what I think James Fennimore Cooper first said in 1831: "They say" is the monarch of the country. It doesn't matter who says it, as long as the public believes "they" say it. We have to think, who are they "they"? Is it the media? Is it us?

And how ought we make decisions? George Campbell reminded us, "Passion is the mover to action, but reason is the guide." And we're all here doing reasoned, evidence-based, but I believe that evidence also means hard--and I'm not saying soft sciences, but the social sciences. How we measure public opinion, as Walter Lippman had mentioned last century, in a whole variety of other ways. That we're goal-driven, thinking of the public health and the people that we basically serve. And then finally, we're using credible, trustworthy, understandable, and emotional and cultural sensitivity.

So what does all this mean? It means what we do here today, sound science and evidence. We

add value with deliberation, debate, and dialogue. And, finally, we're involving a variety of different people in the process, ideally a partnership that I think other speakers have already mentioned today.

But nonetheless, when committees often sit down, we have a sound science and evidence approach. What is the strength of the evidence, and what are the scientific criteria for regulation? Or, on the other axis, how high is the risk? And if risk is so great, we have to regulate or do something specific.

But there's been some changes, as you might know, over the last 47 years or so. It was really just a randomized clinical trial that started in 1947. I mean, it's not like that's been the gold standard for centuries. And now we have new standards, a precautionary principle, which is the axis going down, of where we basically lower and have changed some of the burden of proof.

And more recently, something that is very much of a concern to me is the Thimerosal issue,

and we'll deal a little bit more with that in the presentation. Because Thimerosal, a recent Institute of Medicine committee has issued a different measure of biological plausibility, and whether you agree with where I actually put that arrow, I think we need to think where is that red line and how are we going to be able to continue to do that committee after committee after committee that has different views.

So how do we deal with uncertainty? The precautionary principle has a variety of different definitions. Some people take it down to "It's better to be safe than sorry." Others are saying no, in advance of having complete scientific knowledge, theory testing, basically we're using foresight.

But the changing paradigm has really challenged us. It has challenged us that the burden of proof is shifting. It used to be to make a change you would have to say why something is better than the status quo. Now we have to, for the Thimerosal issue specifically, why is the

status quo specifically bad? Scientific uncertainty, and hence subjective evidence, is in the equation. And, finally, scientists and regulators are requiring evidence now that still needs experimental design.

What can we do? I've been looking at the evidence based on this, not only with my journal, but also I edited a complete current bibliography of medicine with the National Library of Medicine on health risk communication, and there's 847 different articles we found. Institute of Medicine has done about three reports already. But still, nonetheless, we often don't follow the same science base that has been presaged by them, of how we deal with value judgments and how people make decisions about risk information.

Vince Covello has done a lot of this work at Columbia in terms of his Center for Risk Communication, and what he shows us in a variety of different studies with other people is that trust and benefits are looked at as the most important elements. These are not scientific elements of

what the actual risk is, or probability based. This is trust in the messenger. Who is saying it, and what does it mean? And we'll think about that just in terms of the anthrax issue that is all probably still fresh in many of our minds. Myself, living in Washington, I still haven't got my mail that's quarantined.

This is the process, what happens. Policy-makers, experts, opinion leaders and the public are in partnership. And it says here, "Upon further consideration, the evidence of fire is not as strong as first as it appeared. We regret any confusion that we may have had, and will continue to," and you can see everybody stormed out of the theater. This is my segue into BSE, vaccines, and anthrax, and some of the challenges that we face.

I will very quickly go through the BSE issue, because I know I only have 10 minutes. And on the back cover of a book that I edited, "The Mad Cow Crisis: Health and the Public Good," I have these three quotes.

"The biggest crisis the European Union

ever had," according to Franz Fischler.

"The worst crisis the British Government has had since the Falklands," said John Major.

And "If one wanted to study the perils of imperfect policy-making, this case provides them all."

I could probably update. The book came out in 1998. Last year, in 2000, the Frankfurter Allgemeine said BSE was going to be the Black Plague that had not hit Europe yet, and some people still say it's the AIDS crisis that the British never had.

This is, however, a back report looking at it: "There still is no scientific proof that BSE can be transmitted to man by beef, but this is seen by SEAC"--which is the Spongiform Encephalopathy Advisory Committee--"as the most likely explanation, and all our control measures are based on the assumption that it is."

We have continued, and we could explore this everywhere from our TSE Blood Advisory Committees to a lot of different policies that have

changed around the world, this has been a problem of where the scientific proof lies. Above the line here the trade union officials and others are who people trust, and below the line are who people don't trust. And as you can see, the government scientists, the business leaders, the politicians, the government ministers, and the journalists all have lost as part of this BSE issue. This is in the U.K. I don't have data in the United States. We haven't measured it as such, like this. It would be very interesting to see what this all means.

Last, in terms of what the House of Lords report that came out last year reminded us, the government did not lie to the public about the BSE. Government was doing their job. They believed the risks posed were remote. Confidence in government pronouncements about risk was a further casualty. And of course it then says that this is actually affecting everything in the areas of science, including biotechnology and information technology. And the British, later in the report they actually

recommend a committee for the public understanding of science be integrated at the federal level, at the U.K. level, and then in different universities.

I'm going to switch a little bit to Thimerosal, but I'm going to do this quickly because this is very data-rich and it is still, the jury is still out, and part of it is early. You may recall that almost over two and a half years ago, Thimerosal, by part of an act it was released that it was a vaccine preservative that could have exceeded the actual mercury dosage.

Needless to say, a lot of policy happened very quickly, our public health groups, our academies of pediatrics and so forth. And the long and short of it, if you read through the basic pieces, are that Hepatitis B vaccinations, despite that there was vaccine on the market, the real experiment, shall we say, once policy was made, caused thousands of people, of children in this country, not to get vaccinated, and there's already some documented cases. Particularly CDC has looked at four states, one state where there is a definite

death and others that are still there. And this is how it is still ongoing, and right now because of the uncertainty, each state by state is only slowly increasing to levels of Hepatitis vaccination that's necessary. And as you see at the top, it could prevent as many as 5,000 deaths a year.

And I'm rushing through this, unfortunately.

CHAIRMAN LANGER: It's about 10 minutes, if you could try to finish up.

DR. RATZAN: Okay. I'll skip over the IOM stuff, and I just have three slides on anthrax. Who does the public believe in health, in issues of health? And if you see, on the bottom are the people we usually hear from; and if you see at the top, people who people trust, remember that's science-based trust.

And these were the messages that came out in the last three weeks. Most of the messages that came out from politicians and government leaders are below the line in the mistrust area.

This was what Scott Lillibridge said last

week: "We knew that communications would be important, but I don't think we knew it would be this dominant in the response."

So what's the common denominator? And thank you, Mr. Chairman, for another minute or so here. Public health values need to be integrated. How do we do that with societal risk quotient? When we make decisions, how does it play out in society? And if we don't consider communication, we're going to have a fulminating, unintended effect by our policy efforts.

So these are the questions I have and things that we should think about. If we embody an evidence-based approach by providing stringent scientific reassurance related to regulatory issues, we're not reassuring the public(s) that we serve. That's really not scientific. What we really need to do is think about value and trust driven, so we have a common rubric. And I think that this, the field that I am in, is the most humane of the sciences and purest of the arts, and we try to balance both of those.

So these are the five questions: One, could every committee have an expert or someone who thinks about communication or public health, who could add the science of how this most likely will play out? If we make this decision, what will happen? And think about perceptions and practice. There is a scientific approach to this.

Secondly, does the status quo consumer representative that we have on the committees really represent the public, or are they more advocates representing a subgroup of that public? That's an important question to think about.

Can we develop a common metric? And this is something I think is one of the biggest challenges, particularly with all the different advisory groups, not only here in Washington at FDA but all around, and CDC committees and so forth. Can we try to have a rubric for biological plausibility and safety and precautionary principle?

And the final questions: Can we integrate societal risk, that risk is not just for the

understanding.

And I know it's tough to do all this in 10 minutes, and I appreciate the chairman and the committee and the public for hearing me. Thank you.

CHAIRMAN LANGER: Thank you. Any comments or questions? Thank you.

The next speaker will be Dr. Levin from Brimrose Corporation.

DR. LEVIN: Thank you very much for an opportunity. As someone who spent like almost 16 years in a different industry, I wanted to bring a few things from my experience in another industry that can be useful, and then share with you some other information.

My personal belief is that from our history, we will move in this direction for more real-time process control, more real-time nondestructive product testing, and biometric release. I believe it's going to go there because I think it doesn't have an alternative. The expected results will be high product quality and

security, substantial cost reduction, benefits to shareholders, and benefits to the public, universal drivers.

Can we learn from other industries? I worked 16 years in the aircraft engine industry. Both industries hold people's lives in their hands. You fly up in the air, you are in their hands. You take a drug, you are in their hands. Both are federally regulated. They are very competitive. They drive their products with strict performance limits. They are being chased by generic products behind them. They are also driven to lower prices by government and by the users.

Okay, very quickly, aircraft engine industry in the '70s. Product testing was the major quality thrust, backed the product. Pratt & Whitney, incoming house testing lab, 600 people. Ratio of inspectors to operators, two to three, about. Operators not responsible for the quality; the inspectors are. Statistical process control, nonexistent. Scrap factory, 20 to 30 percent of the total volume production.

In the early '80s they made a change to active and statistical process control, became a major Total Quality Management. Pratt & Whitney incoming, in-house testing, down to 100 people worldwide. Ratio of inspectors, about one to eight. This is a huge savings, cost reduction. Operators now become responsible for the quality, not the inspector who is supposed to catch something. Scrap factory down to 5 to 8 percent, it's going down. Quality increased, engine failures became rare. This week I really got scared, because what if this American Airlines was downed by an engine, but it was not, so I kept this slide in.

[Laughter.]

But I really got scared. Cost, dramatic reduction. Typical cast blade, I was involved in this technology, is now 3 to 4 times cheaper for the cost but the quality is much higher.

Where is the industry today? I think I can skip this one because you were already told where we are today, so I don't need to say much

about it. Still product testing, on-line active process control is still minimal. I don't know what the range of QC to operators are, maybe one to two, I don't know. Statistical process control, I was told practically nonexistent. I don't know what the scrap factory is, but you were told today it was about 20 percent, something like that. Still too many recalls, 200 about a year. Product uniformity still an unresolved issue.

Can we learn? Yes, we can, because the drivers are the same drivers for the change, the government and customer, pressure to reduce cost to operate, competition, performance, pressure to maintain profitability for shareholders, sense of "dead end" in doing more of the same. This is a huge driver. And the thing that today we see that there is a sense that if we keep on doing the same thing, more and more and more, it's a dead end. And the FAA provided strong support, anticipating the benefits to the public. Being a Federal agency, they thought about the public, and it's their duty.

The conclusion that I draw from that is that the pharmaceutical industry will follow the same path taken by the aircraft engine industry in its bid to be more cost effective and, above all, more profitable. After all, you got to make money; otherwise, nothing happens, and we know that. So the facts are, same drivers, the FDA is providing now increasing support, realizing the benefits to the public, and we have Ajaz and other people, and the industry is getting again the sense of "dead end."

How? The question is, how we going to do that? And there is more than one tool, and we have seen some of them, but I still think that NIR is probably the most significant, and as success will create new and improved tools, soon we will not be able to understand how we could do it otherwise.

Why is NIR so important? I think it is the only tool that really provides significant chemical and physical information on the bulk of the product, not just the surface. It is the only method that penetrates tablets and capsules for

complete characterization. And it provides information on all ingredients, not just the active. Is a tablet good if some excipient missing? I think it's not. If it was there to begin with, it's supposed to be there when I take it, so I like it to be there.

Sorry, forgot to turn mine off.

DR. NEREM: That's your timer.

[Laughter.]

DR. LEVIN: No, no. Sorry. Forgot to turn mine off.

Why is NIR, once very quickly, why is NIR so good? Because it penetrates. The light that goes into, either into reflectors, into powders made in a blender or any other operation, it penetrates to a depth between 2 to 4 millimeter. It doesn't just scrape the surface. That's why it is so important, being a tool that tells us enough information on the bulk of the product we are processing.

Now I'm going to represent my company. I don't own it. Why then is NIR so important? It is

very fast, and people say today we need speed. It is simply rugged, and it was tested dropping on the floor, kept on working. It's a dual beam for real-time ratio, so we don't have to stop anything for taking some reference spectra from some reference sample to do some adjustment. It is always dual beam, giving real-time ratio.

It is full scanning, to provide information on all the ingredients, not just the active. It comes with a full computer on board, so you can process as many algorithms as you may want. And it's miniaturized to do blenders, battery operated, you will see immediately. It is insensitive to ambient light variations, so it can operate in any ambience without any consideration to what's happening around. And it is backed by 21 C.F.C. 11 tested from Brimrose.

It's important because I think it's the only analyzer that can do them all from one company. We can do incoming raw materials, fluidized beds, rotating blenders, tablets and capsules, various lyophilizers, spray dryers,

blister pads, transdermal patches. So you have a company that has one source for every possible application that you may want. Why would you want to go and use application A from manufacturer A, application B from manufacturer C? We will provide complete solutions for every need.

I turned it off, I swear I did.

CHAIRMAN LANGER: Now I think it's getting to be the time.

DR. LEVIN: I turned it off, I swear.

CHAIRMAN LANGER: Dr. Nerem reactivated it.

DR. LEVIN: This is all the material I need, but we also have ability to connect it to a multiplexer, so you can have a multiplexer for doing more than one location with one analyzer.

This is a typical installation in a fluidized bed. You can see the globe, but we have done these fluidized beds not only with globes, we have done fluidized beds with what we call the free space, and we have an installation running now in New Jersey on that.

elw

This is our miniaturized spectrometer. It has two batteries. It's only 18 inches by 16 inches by about 4 inches. It has got a complete computer on board, so you can process more than one algorithm. It can be mounted on blender, it could be mounted on fluid bed dryers, it can be mounted against a bio line if you want to test bios, if you want to do reflectance on tablets.

CHAIRMAN LANGER: We're at 10 minutes. Can you wrap it up in a minute?

DR. LEVIN: Yes, just one more slide. And this has radio transmitter, this one has a radio transmitter to stop the blender. So all the processing of the data is done on the spectrometer. We don't need to transmit data.

To the last one, I think. This is a tablet analyzer doing final testing before shipping. You can see again the whole spectrometry is in this case. It is operating on 24 volts coming from this cable, and has internal cable to connect to a site computer, but during operations you don't need the site computer, because actually

during operation you have a model, an algorithm that you use on the spectrometer for decision-making, and it links the, connects the decision to some other. This connects automatically to a tablet press, and it sees the tablets from the press without the contact of hands, so it's automated and can be stored in a remote room or anywhere else.

I think that's the last one.

CHAIRMAN LANGER: Well, it's the next to the last one, but we're at 11 minutes. Why don't we wrap it up?

DR. LEVIN: This is a typical multiplexer. That's it. Thank you.

CHAIRMAN LANGER: Any comments or questions? Thank you.

The next talk is by Robert Chisholm from AstraZeneca.

MR. CHISHOLM: Good afternoon, everyone. My name is Bob Chisholm, International Technology Manager for Engineering Science and Technology for AstraZeneca, and I am based in the U.K. First of

all, I'd like to say how pleased I am to be back in the U.S.A., in Washington. Unfortunately, it's only for one day, but it's very, very nice to be back here.

What I would like to talk about I hope will supplement and complement some of the excellent presentations that we had this morning, and maybe help you answer some of the questions that I've heard posed. I'll keep this down to 10 minutes, so I may speak very quickly in my Scottish language, so you may find that incredibly difficult to understand. So if I need to slow down, tell me to slow down.

What I want to talk about is TQMS, which is the AstraZeneca Total Quality Management Strategy in our facilities, and it's a very statistically based end process control with real-time quality assurance, and it's about a plant that we have designed and built in Germany, and I'll tell you all about that.

What do we do just now in pharmaceuticals? Basically, traditional QA means that we validate

processes, the usual three batches, etcetera, etcetera, and then we run them under standard operating procedures, virtually no end process control for a long number of years. We supplement this, of course, by testing a very small number of samples at the end of each batch, and that's our QA assurance, and typically that could be 10 samples out of a million, two million. Taken in isolation, clearly that is not statistically significant.

The way forward, I think, for future products, the way we would like to go, is TQMS, which you have heard a lot about, I think, already. It's real-time end process monitoring and control which is being made continuous, and its real-time quality assurance which is statistically based throughout the batch.

In our particular case that would be done automatically, but you could also do it at-line, so you're taking samples all the time. So you actually have an increased testing frequency, and that increased testing frequency which is statistically based, provides you the platform to

discuss with regulatory authorities so-called parametric release. A term which I don't like, by the way, because we actually increase the testing, not decrease it.

Okay, how do we do this? Well, I think first of all in any pharmaceutical company you've got to have the sponsorship of your senior executive team or you won't succeed, because it is often harder to change your own company than it is to talk to any regulatory agency, believe me. There's a lot vested interests in the companies. This is a paradigm shift, and if you don't have the cooperation of your own board, you can forget it in the industry.

We have created a process on what we call Technology Center of Excellence, which is based in Sweden, and they are looking at the whole range of methods, not just near infrared, and the product development using these methods. But the thing I want to talk about today is related to the Center practice. We have built a plant in Germany, in Plankstadt, which we sanctioned early '99, and we

have integrated TQMS at this plant, and I'd just like to show you that. So this does actually exist and goes live on December the 1st.

Okay, what have we done? Key process operations are now statistically in process controlled and monitored, so that identification of all raw materials in the dispensaries, things like control of fluid bed driers on line, continuous end line monitoring of blending similar to what Steve showed you earlier on--okay, and that's end point control of blending. What that does, that's in process control. That ensures that everything that you put into that tablet press is in spec and is the way you want, and the blend has been correct every time.

We then have the tablet analyzer automatically within the tablet press, and again it's looking at the tablets which are going through check, so it is monitoring tablet quality throughout the batch. That in itself is a big paradigm change for the industry. We've also designed a 21 C.F.R. 11 data management system to

go along with it, because with all this data on all these spectra, compliant data management is clearly of the essence. And through that, we believe that we have real-time continuous quality assurance.

This is the actual architecture, and it's so complicated on this small screen I can't see it, so I'm going to have to just talk to it up here. If you look at this, you'll actually see that the analyzers we've used are by Brimrose, because of the OTF. You'll see there are four Brimrose analyzers which run the plant.

If you then look on each analyzer, you will see a panel PC and you'll see actually a bar code reader also on there, which is attached to each measurement. And these are managed by an NIR server on the top there, and all the data is reflected to what we call the PacMan server, which is a system for storing this data in a correct forum which was developed by our colleagues in Astra.

So to give you an example, in the dispensary for instance, the operator would come

along. He would log onto his panel PC, using his password, because it's 21 C.F.R. 11. Having done that, he would then take the bar code reading, so the batch attributes, hence the panel PC, so it has the operator's name, all the batch attributes.

The panel PC then contacts the NIR server, which enables the analyzer to do the correct measurement and puts any models, etcetera, down into the analyzer. He takes the measurement, the panel PC gives him the result, and then all the data is automatically transferred from the analyzer via the NIR server into the PacMan system, so it's in there for inspection by regulatory authorities or anyone else, for that matter.

The way we have designed this system, by the way, it's also capable of being inspected remotely through modem. So someone could sit in Washington, connect to the modem, with our permission, of course, this is complete openness, and actually look at that plant as it's running to check the compliance, which could be a thing for the future.

Okay, just moving along, you'll see we have our fluid bed drive analyzer there, which is a dryer end point control. That's actually the one multiplexed analyzer. We then have the blender analyzer, which sits in a base station, comes off the base station, is mounted onto an IBC which is spun, and looks through the sapphire window, tells you when the blend is finished, stops the blender. When you put it back on the base station, the data, the spectra, automatically again transfer through the system into the PacMan system. That's all for regulatory authorities or anyone else to inspect.

Okay. And, moving on to the tablet analyzers--I'm trying to watch the time here and keep this down--there are two tablet analyzers, two tablet presses. We have only put one in at the moment because nobody really believes all this will work, and that's the problem with the industry, I think. But I come from ICI Petrochemicals, and was very, very used to doing all this sort of work, so it's second nature to me and my team.

Again, the tablet analyzer, it's using

transmission and reflectance, and all the data is transferred up and stored in PacMan, the same as with the other systems.

Okay, now I'm not too sure what other slides I've got in here. I'll just try them. Oh, yes, that's just a schematic, obviously, of the plant, and that's a solid dosage facility, which you'll all be aware of. That's an example of an IBC with the blend monitoring unit actually mounted on it. This only 120 kilograms. That's why the IBC looks so small. The whole system just spins together there.

A tablet analyzer. That particular one I think is the one in the lab. You need to have them in the lab also, because you need to model, and it's much easier to model with it in the lab. But it's connected up to use on that system just the same, and is the analyzer that actually sits in the tablet press. And that's it actually in the tablet press, I bit difficult to see, I think, but the box here is actually the analyzer, the tablets coming off and going down to be analyzed as they pass.

Okay, that's what I wanted to say to you. As you see, that plant does exist, so the industry is moving forward. In terms of the actual way forward, our intention would be, listening to this morning's presentations, our own intention would be to obviously start talking to regulatory authorities. I'm a bit premature here. The opportunity arose.

We would chose one of our existing products that we make, which we have five years say operating experience of, so we have lots of means of comparison. We would model with that. It would be our intention then to run parallel dossiers, because we can run the plant with or without the system. So we would run near infrared and run all the existing registered systems, and compile parallel dossiers, and then bring that to regulatory authorities who we should have been talking to, will talk to all the time, as a means of comparison. So if you like that as the sort of pilot project that I think someone mentioned this morning, then that would be our intention.

So that's all I have to say. I've cut it down, obviously. That's normally a one-hour presentation. But hopefully I got enough over to let you know what we're doing. Okay? Thank you.

CHAIRMAN LANGER: Thank you. Are there any questions or comments? Any other comments from anyone here? Yes?

MR. WOLD: Yes, Svante Wold from Umetrics. I just want to emphasize one thing, and that is that we see a lot of very nice technologies, and that is essential. You have to measure the right data. But one also has to tie everything together. You have to have, as in the last talk we heard, a data-based system, and you have to have tools to follow all these data. Otherwise, it just becomes a data cemetery. And there exists technology for that, too, and that is what we presented. Thank you.

CHAIRMAN LANGER: Any other comments?

Okay. Well, thank you all very much. We'll move on now, and we're going to get an update on the CDRH External Science Review. At the end of

this, we need to vote on acceptance of the report at the end of the presentation, and Dr. Nerem, who was Chair of this, will lead the discussion. Bob? This will be about a two-minute thing?

[Laughter.]

DR. NEREM: Actually I was going to use this time to sell coming to Georgia Tech to do your educational program.

[Laughter.]

CHAIRMAN LANGER: We'll make sure that's on the next Science Board agenda.

DR. NEREM: Well, it's a pleasure to be here and to represent the committee which produced this report, which we ended up titling "Science at Work in CDRH: The Role of Science in the Regulatory Process." The next slide actually shows the members of this committee. I'm not going to go over it in all the detail, but I do want to recognize and introduce Alexa Canady, who was my Co-Chair and who is here to make sure that I'm honest, I think. But it was an amazing committee, and I believe FDA and CDRH really owe a vote of

thanks to all of these people who just performed in a marvelous way.

In addition to a note of thanks to my committee members, I want to thank the CDRH staff members who worked closely with us. Of course that was at a variety of levels. There were people that really made it happen, and that includes Toni Marie Nearing who is sitting over here. Toni, thanks for all you did. I see Sandy Weininger out there, who helped--I was going to say helped write the report, in fact should be listed probably as a co-author, but he really was very neutral in his approach to what we did. I see Mitch Shein back there. And there's another person, I don't know if he is in the room. Is Heini in the room somewhere? I don't think Heini is here, but he was also extremely helpful through the entire process.

And of course we want to thank the entire management of CDRH and the staff who participated in the internal/external reviews. I think all told there must have been somewhere on the order of at least 150 people, and maybe there was more than

that, David. I don't know.

Our objective was really to assess the quality of science across the organization and its relevance to the organization's regulatory mission. We were not put together as a committee to evaluate the research going on within CDRH, but really to look at how science was playing a role and how it could play an even more effective role in regulatory decision-making in CDRH.

This is an outline of the report. I won't go over this in any detail. I'll talk a little about process. I'm going to come back to process at the end; talk about the findings under these three categories; our recommendations; and then some concluding comments.

There was an internal review process. I think one of the key issues was that it was decided early on by CDRH that electrostimulation devices would be chosen as the representative technology. That is really where we focused most of our work, although we believe that in fact much of what we found can be generalized to other parts of CDRH, in

fact can perhaps be generalized to all of FDA.

The ground rules are indicated here, and I'm not going to go over that in any detail, but I do want to take this opportunity to commend CDRH for the substantive nature of the internal review and the spirit in which it was conducted. I really believe that internal review, which was a time-consuming process for CDRH, provided the foundation for them to move forward as an organization and for us to come in as an outside group and get some insight into what could be done in the future.

In terms of the external review process, I have already indicated that built on the knowledge provided by the internal review. There were really three different meetings, all of which were important, in my opinion. The first was a preparatory meeting held in Atlanta, where the External Review Committee came together and where we really sort of sorted out what we were about, and in fact we made some assignments at that time in terms of some of the case studies that we would be involved in.

There was then the three-day review held in Rockville, July 24, 25, 26, and then finally a good part of the committee came together for a one-day report writing session on August 8th. At the three-day meeting, we began to put together the outline of a report. We made assignments for different sections of the report, but the report really came together at that August 8th meeting, and then we had a final draft this past month.

In that July 24-26 review, there were the case studies; there were role-playing session, both for pre-IDE and post-IDE; there were omsbud reviews; industry interviews; and in fact international interviews. The international interviews being, number one, we had Beth Pieteron from Health Canada on our team, so we could talk to her directly. But we also were hooked up by video conference with David Jefferies in the U.K. to get a perspective on what was going on in Europe.

Now, under scientific expertise we break down our findings into these different areas, and I'm just going to highlight some of the findings.

The complete report is available, as well as a copy of this presentation. So let's move to the next slide, John.

And in terms of the findings, I mean, to start with we certainly wanted to go on record as reaffirming that good science is critical to good regulatory decision-making. Furthermore, as I think we all recognize, the complexity of applications requiring review has increased and will continue to do so.

What was evident to us was, in general, the overall high quality of reviewers, medical officers, scientists, engineers. Even so, the expertise across fields is uneven, and that's something I'll come back to. We also felt that perhaps the level of expertise among staff about the clinical environment, at least in some cases, was limited.

Continuing with the section on scientific expertise, we felt that there was not enough emphasis placed on the quality of decision-making as compared to the timeliness and volume of review,

and I'll come back to that in the recommendations. Furthermore, there appeared to be a strong tendency for the Office of Device Evaluation to operate primarily in-house, and as indicated there, we felt that was at least what was happening in fact, whether it was not by plan, but certainly that was our perception of the way day-to-day business was being conducted.

We were very interested in learning about the use of third parties in other countries, for example, the notified bodies in Europe. And as we look to the future, we have a concern as a committee whether CDRH or even FDA as a whole has the right expertise for the evaluation of combination products, those products that will be a combination of a device and a drug, a combination of a device and a biologic, or whatever.

Moving to the next section of the report, which is the human resource issues, it's organized by these different categories, and let's go to the first slide of findings, John.

Again, I want to note that we were

impressed with the quality, professionalism, and dedication of the staff we encountered. However, it's clear that there is a gap between the scientific expertise needed and the competencies of the current staff. There also is a woefully inadequate investment of resources and providing of opportunities for staff training and development. There are clearly too few staff to carry out the necessary activities as CDRH now functions.

And for CDRH scientists, people who not take the track of management, it seemed to us that there was a lack of promotion opportunities, at least opportunities that could be somewhat rapidly taken advantage of. The process apparently to be promoted as a scientist was a rather long, extensive one.

Moving to the organizational and process issues, again the report is structured along these lines, and let me just say a few words about our findings.

To start with, we characterized CDRH as an organization that was basically "semi-porous

silos." I suppose the good news is, they're semi-porous. We're not quite sure how large the pores are. But there needs to be attention paid to that.

There also needs to be attention paid to metrics about quality, for as far as we could tell, there appeared to be no quality metrics about CDRH as an organization or even necessarily the decision-making process. Certainly there seemed to be no system of retrospective measurement and analysis of specific CDRH decisions.

Now, in the case study that took place as part of the internal review, in fact that's one of the things that took place. There was some reflective looking at things, but that does not appear to happen on a regular basis.

Also consistent with the semi-porous silos is the fact that there is no effective interoffice communication and coordination. Furthermore, external experts are seldom used beyond those who sit on existing FDA advisory panels.

And in the case of combination products, there is no clear pathway or guidelines for the

regulation of these products. There is really no single entry point for these products.

So moving to the recommendations, recommendation number one is that CDRH needs to communicate, both internally and externally, a clear vision of the fundamental role of science in the regulatory process.

Secondly, it really needs to rethink, in our opinion, how it carries out its mission, prioritizing its activities, outsourcing those functions it can, while still maintaining oversight, and reallocating its resources so as to expand its investment in science. And as part of this, CDRH should examine its existing organizational structure as well as other regulatory models.

As part of its restructuring of activities, recommendation three is that to enhance the fundamental role of science, CDRH should assess and reconsider the structure of the Office of Science and Technology, to focus that office on emerging science and technology. This will

probably require a separate review of OST, but we believe in fact that OST should be that part of CDRH that is really leading CDRH into the technologies of the 21st century, and that we believe requires some restructuring, but since we did not have a chance to look in depth at OST, we feel a separate review is in order.

CDRH should develop a plan for enhancing cross-office and interagency communication and collaboration.

The next two recommendations, five and six, really come to information technology, and that may be a problem for FDA as a whole. Certainly there should be an electronic database for liaison functions and an internal and external expertise inventory. Furthermore, we believe that CDRH should develop and implement a formal process for capturing institutional knowledge, so that when a decision is reached it does not remain in the mind of the reviewer.

I think an important recommendation is that with the large staff turnover anticipated in

the next five years, and in order to fill gaps in scientific expertise, CDRH should expeditiously perform an assessment of the current level and breadth of expertise so as to develop a long-term strategic staffing and recruitment plan. As an organization, it really should be looking at where it needs to be five years from now, what kind of expertise is going to be required, and develop a staffing plan that is going to allow that to take place.

There also needs to be the development of procedures and staff development opportunities to ensure that reviewer mandates for such issues as sample size or randomized trials are shaped by realistic clinical perspectives and relevant ethical considerations.

Recommendation nine goes back to a comment I made earlier, but that is that CDRH needs to streamline processes that encourage scientific growth within the staff and provide for a more inviting career path and reward structure for scientific personnel, people who are not moving

into management but are valuable as scientists within the organization.

There also should be an encouragement and the facilitation of ODE using internal but non-ODE expertise, and also external expertise, including the development of policies that promote a more liberal use of external experts.

As part of this, CDRH should expand its outreach to and scientific interactions with both industry and universities.

The final three recommendations are that CDRH should develop a plan in collaboration with other Centers for the evaluation of combination products. This plan in fact may require changes in organizational structure and operational procedures.

Number thirteen and fourteen really go together, really relate to quality improvement. Thirteen is really more at the regulatory decision-making level. CDRH should implement a quality evaluation improvement program, and as part of this develop metrics for the assessment of quality as

well as the timeliness of results.

Fourteen is, at the organizational level CDRH should implement a quality system with a focus on CDRH as an organization, and on development of activities that contribute to high quality decisions and the most productive use of resources.

With this, let me say a few words about the process itself. These may have a bias of my own. David Feigal and his office actually sent out a survey form, and I think they are reasonably consistent, but this is my take on the process.

I believe that the review, in focusing on the role of science in regulatory decision-making and not on scientific laboratory research, that that was the right focus, and we recommend it to the Science Board for use in future reviews. The deliverable of an organization like this is not good research; the deliverable is good regulatory decision-making, and I think that needs to be the focus of these reviews.

The internal self-study not only provided

a foundation for the external review, but was a significant learning experience in its own right. The external review, as I noted earlier, had three separate meetings, and I believe that each of these meetings was critical. The pre-meeting in Atlanta really allowed the review team to get organized into how they were really going to conduct their work in a three-day period. The three-day meeting in Rockville allowed us to carry out the review, and the final meeting on August 8th allowed us to complete a reasonable first draft of a report.

In terms of the components of the process, I thought the case studies were important to our success, and also the fact that we assigned at the initial preparatory meeting small teams to investigate each case prior to the three-day review.

The role-playing, my own view was that the role-playing was not as effective as it might have been. I don't really feel like the committee ever got into the role-playing. I don't know how Alexa feels, but I just didn't feel that we really put

ourself in the roles we were supposed to.

The on-the-spot reviews, that was basically where we could get any information on any kind of a review decision that had been made, and it was difficult in a way to intervene in that and get something. At the same time, CDRH was offering us everything and anything, and just that gesture by itself was a very clear signal that they were open to us looking at any aspect of the operation, and I think that was an important signal.

The industry interviews were important. Unfortunately, they weren't all face-to-face, and I think in the future if this kind of model is used, it needs to be clear that these need to be face-to-face, these discussions with industry people.

The international interviews, we thought that was quite useful, both having Beth Pieteron on the committee as well as the teleconference with David Jefferies. The CDRH management and staff meetings are equally important, and we did, particularly in the case of the case studies, during each of those meetings we asked senior

management to leave so we could meet with working staff without management in the room, and we believe that was important in terms of creating an environment where there would be a totally honest conversation.

We also had a meeting with the union management. I think that meeting could have been much more useful if it had been organized well in advance. The fact of the matter is, it was only at the last minute that we asked for the meeting, and there wasn't the same preparation, both on our side as well as on the union management side, and so therefore I don't think it was as useful as it could have been.

Some concluding comments. I again want to commend CDRH for the dedication, integrity, and commitment to excellence exhibited by this effort. In many ways CDRH is doing an excellent job. Even so, with new products arising out of the biological revolution, with breakthrough technologies which will be increasingly complex, CDRH is facing a significant challenge.

We felt that this review was conducted in the spirit of trying to be of constructive help to CDRH as it faced up to these challenges. From the viewpoint of the committee, there clearly are changes necessary if CDRH is to significantly increase the role of science in regulatory decision-making.

This slide really has what I think are, of all the recommendations, what I think are the three key things. First, I really think there has to be a rethinking as to how the business is conducted. Again, what do you do in-house, what do you farm out, what are the priorities, how do you get your hands around science and technology, which every day expands further and further.

Secondly, as part of this, as part of this reinventing of CDRH is a reinventing of the staff through strategic recruitment, the continuous professional growth of existing staff, and policies that reward staff for the quality of scientific expertise. And that goes back to really creating a long-term strategy for recruitment over the next

five years.

CDRH must reach out to external resources to create partnerships that will accelerate making new technologies available that are both safe and effective, and so as to enhance patient benefit in America. No organization can have all the expertise, and I think CDRH needs to more and more use external expertise.

Finally, the subcommittee review team appreciates the fact that these recommendations, even if accepted, cannot be put into place overnight, and certainly the way to go would be to incorporate these in some active way into the strategic plan of CDRH.

I think that may be it. Is there another slide?

Okay. Thank you for this opportunity to present the report, and again, thanks to everybody who worked with us. And I don't know if you want to open it to questions or whether you want David to have a chance to--

CHAIRMAN LANGER: What do you prefer?

DR. NEREM: I'm easy. But I'm glad you asked about Georgia Tech, Bob.

[Laughter.]

CHAIRMAN LANGER: Maybe I'll let David present. There will be many questions about Georgia Tech later.

DR. NEREM: Well, particularly since we're trying to get David's son to come down to Georgia Tech and be a student. Right, David?

DR. FEIGAL: Well, I need to begin by thanking Bob and Alexa and the other 10 members of the committee that joined them for the tremendous amount of time and the thoughtfulness of the effort that they put in, and I think you probably all appreciate how busy Bob is likely to be, but part of the reason we met in Atlanta for the kick-off meeting was, that seemed to be the only way to accommodate Bob's schedule, and we were interested enough in getting this to move along and get things, that we were happy to travel down there and begin with the orientation.

This report comes at a very important time

for us, because it's coming at a time when we have been working on a strategic plan to ask how do we meet the challenges of the future, and I have presented bits of that to the Science Board before. Part of that is a vision that the Center has, that medical devices have a life cycle; that the whole life cycle is informative in the scientific decisions we made; that in fact it's a pipeline of multiple generations of products.

There is a regulatory structure that surrounds that life cycle, but what we really were asking the team to do was to come in and look at this. And what this is, it's the underlying science that we think is necessary to do science-based regulation at the different parts of the life cycle, for all the different regulatory tasks that we have. And our focus and our interest was not as much about asking how we got here or why we were the way we were, but really looking forward and saying how do we need to go from where we are now into the future, and I think that we appreciated the very constructive approach that the committee

took in helping us think about that.

Let me pause just for a second to show you, somebody had said something about the Center. The room was pretty full this morning but it wasn't the same people. Would everybody who works for the Center stand up? This is a group that--you can sit down now--we are very, very interested in where we're going and the help we have getting there and the comments, and it's a process I think that, Bob and Alexa, you realize we take very seriously.

As you pointed out, this began with a planning process that began in November of '99. It was helpful to me as a new Center Director. I had started about six months earlier than that. Unfortunately, now I've been there long enough that many things are my fault. If we had had these recommendations just as I arrived, I would have felt even better, but that's all right. We'll move forward.

And where we are today is near the bottom of this chart, and the important thing, part of what I want to show to you is our strategy for

implementation. But before I do that, I actually want to share some of the things that we did, that you alluded to, with our internal report process. It will give you an opportunity to see whether or not we were on sort of some of the same tracks that you were, because I've taken the documents, unedited, that we provided to the committee when it first began to meet.

As you pointed out, we really were interested in the scientific decision-making process. We think that is our most fundamental product, our decisions. In fact, if you hear complaints about us, it's that we haven't decided something, and then the second complaint is what we did decide. But we're in the decision-making business, and it's important that we understand the impact, the resources that are required for this to be a science-based process, how well those decisions are integrated with all the different processes that we're responsible for, and how the organization learns from the way that it does its work, and our preparedness for future issues.

I'm a little sorry that Dr. Skulnick isn't here, because you remember at the last meeting he said, "Why don't you give us the top 10 list of the best things about the Center and the worst things about the Center?" We in fact actually provided a slight modification of that to the committee as a product of the internal review, and I'm presenting this as one way of summarizing some of the work of the internal review.

We presented a top 10 list of the greatest challenges and problems for science-based regulation at CDRH, and then we also made recommendations of what we thought we had to do to address some of these. And it may be interesting for you, having heard the External Committee's recommendation, to take a look and see how self-aware the Center was or was not about some of these issues. In the notebooks I have presented these just on one page, and I've broken these out and organized them so that the challenge is met with our own recommendation.

And so our first observation was that

we're not always recognized as a science-based organization, sometimes not even by parts of our own structure in FDA. It certainly is not a novel experience to have Health and Human Services organize a scientific group and leave us off. When they organized the task force for the Biomedical Engineering Institute at the NIH, they put together a Public Health Service Advisory Board, and FDA, CDRH was not included in the PHS group that was to advise the NIH on the scientific needs. Congress at times really is very--well, they're always very aware of the freight that we need to move, but they're not always as aware of the scientific basis of that, and at times that's true of industry as well.

So where we began with our first challenge--and these are in rough priority order--was that we need to communicate our scientific vision and the scientific business for our regulatory actions. It isn't adequate to simply say we're doing something because of precedent or level playing field or because we said so. We need

to make it clear that these are science-based. We also need, and this is a request from you, we need advocates for our scientific role in medical devices and radiological health, and there are ways that you have been doing that.

The second comment that we made when we were being self-critical of ourselves is that the Center leadership, meaning me and the senior people in the Center, do not always communicate science as a priority. I think we're always quite clear about meeting performance deadlines in some of the goals, particularly the ones we report to Congress or with a trade press or an industry track.

But we miss opportunities to create the resources and time for our scientists to have the training. We don't create the expectation in our own staff that part of their job is to stay at the top of their game and stay current. And the budget in our resource planning has often been reactive and short-term, and we need to walk the talk and show that science is really a priority to us. Our recommendation sort of is the mirror of the

observation.

We are also very aware of the fact that the CDRH's scientific staff is graying. This year we actually saw the retirement of the employee who was the longest working employee for the agency. He has worked for the agency for 62 years, and I hope he's enjoying his retirement in Florida. But one of the real challenges for us is that there are time when we go through waves of hiring and long periods without hiring, and that gives us waves of retirement, and this is both a challenge and an opportunity.

And one of the elements of our strategic plan is one that we call Magnet for Excellence. We borrowed that concept of being a magnet from the magnet school system. We really want to be able to attract the type of employees that want to help us accomplish our public health mission. And I really resonate very well, Bob, with your phrase "strategic recruitment." We really need to not just think when we lose someone, even though that person was doing valuable work and had built up an

in-box that now needs to be taken over and a specific area of expertise, we really need to look and say "What do we need now?" That person was hired at a time when we needed that. And we need to think about what the process is, because if we just backfill position by position by position, we will be configured the same way in five years that we are now, so we need to think about how we're going to do that.

The budget policies of the last eight years markedly reduced our operating dollars, as we were absorbing the salary increases, and the good news that you heard last night from Jeff Weber is that in this year's budget in fact we don't have to absorb 4.6 percent of our staff in order to pay for the appreciated pay raise, but it's even more appreciated when they give us the money for it.

But I think the concept for us is that it really doesn't matter if we're rich or poor, we have to have the same scientific values and the same approach to scientific problems, whether it's a year where we have some budget flexibility or

some budget challenges. And we need to really look at how to take care of our existing employees to make them as effective as they can.

There was a very nice comment by one of the members of the Science Board who couldn't be here today. Earlier this week there was a meeting at the University of Maryland. I think they beat Georgia Tech, didn't they this year, Bob? But there's always the basketball season. We'll see how this goes.

DR. NEREM: We're even better in basketball.

DR. FEIGAL: But the comment that was made is that art is "I" and science is "we", and we really train people almost as artisans, as apprentices. They work with a small team. They learn what that team does, how it works. We really need to take the strength of the scientific method, which is really a group process, a process where everyone learns from each other, we need to identify much more systematically, particularly with employees whose jobs are changing, to identify

the core competencies and the type of experiences that will develop them as scientists and create flexibility in our scientific work force to meet future challenges.

Our current system actually tends to have a system where people almost need to burrow in to get promoted. If you're not going to be a supervisor, then you need to become an expert, and an expert often is someone who--it's more of that "I" model, where you are the expert. You are the one that has the knowledge and doesn't share it. And one of the things that has happened as part of the strategic plan and part of our grappling with this, is that we have actually created and gotten approved a program called the Master Reviewer that supplements the expert path, that rewards breadth, and a different type of experience for promotion. It's a program that Janet Woodcock had in CDER, and then we have actually crafted our own version of it which is just now being launched.

There is the very real fact that premarket deadlines, acute problems, squeaky wheels, meaning

any type of, sort of contentious situation, often dominate resource allocation in a way that can leave programs disconnected and sometimes out of balance. One of the hardest things for us to figure out is, what's the right size for different parts of the unit, because everyone is busy and everyone could do more with more resources. And are we just putting it where Congress squeaks or where a group of manufacturers create a lot of public attention?

We need to have our own vision of sort of the public health mission, and be able to balance and prioritize even through that. Even though we must meet these deadlines and must deal with these problems as they come up, we need to more deliberately prioritize our work proactively, rather than just being reactive.

Scientific communication opportunities are under-utilized, whether this is with our scientific peers, whether it's medical device users or the general public, and this hides what we know. It hides the knowledge that we in fact manage, and

limits our mission effectiveness. And so one of our real goals is to understand better. I really appreciated the earlier public presentation on risk management and risk communication. That's something we think a lot about. And the public's hunger for knowledge is illustrated by the fact that nearly a million people will read the Lasik web site this year.

We solve many problems too slowly in a rapidly changing world. Some of our decision-making is timely, particularly the ones where the rules are set out in advance that say, "You send us this kind of application and we'll review it in that many days." But there are other kind of problems that are much more difficult, and we need to really be able to set goals, choose important problems, assess how to measure the impact in those areas, create the team needed, and then be accountable for timely results of the efforts. And we're going to need to learn to prioritize and do that.

We agree with your comments about the way

that people's work is reviewed, whether it's the quality or the impact of the decision. Peer review is under-utilized as a method for prioritizing our efforts for evaluation. And usually when we do evaluation, it's through the usual hierarchical supervisory structure, and I think this actually misses an opportunity for people to be reviewed by their peer, to look at the incorporation of science into the decision-making.

I think that this is all the more important as we make the results of our decision, not just the decision itself but also the logic behind it, as we start publishing our summary basis of decisions. You know, the science is laid out there bold for everybody to see, and we need to take advantage of that.

And then finally, and again I think is very concordant with one of your recommendations, scientific partnerships with the NIH, the National Academy of Science, universities, professional societies. Many of these exist, but they are under-developed. We could do much more with them

than we currently do.

And so that was our top 10 list and our 10 recommendations that we gave last spring. We put together sort of a different structure for this review, and we were sort of making it up as we went along. And so one of the things I would be happy to show you is the survey that Dr. Nerem alluded to. All 12 members would have responded, but one was on travel and couldn't be reached. And this is in your packet, in a handout we gave at lunch time in a tabular form that I've reformatted for the slides.

One question was, was it the best thing to open the scope of the review to be the entire Center and not, for example, just to limit it to the research programs. And that, after the fact, after the review was over--this was a five-point scale where the green at the end is a five and blue is a four and yellow in the middle is a three and so forth--and so you can see that actually that was a concept that resonated well with the committee. They agreed with you that the meeting in Atlanta

was useful, and a complement to many of the people here in the room, that the background materials on the mission and organization that helped jump start that process were useful.

Case studies. We asked separately about the concept because we weren't--we also, particularly as we looked at the different ones, there were different levels of execution. I think the committee got a little better into the pre-IDE one than the post-marketing one. And the most useful thing, and you'll see this theme again, was being able to have access to interview them about the process. Materials, they are, I mean these are complementary marks, but clearly the staff interviews were the most valued. And the concept by and large seemed to work, whether or not--you know, I think we could have improved the execution, and some of the problems at times was trying to get it all crammed into three days.

On-the-spot concept didn't work as well, and the committee agreed with you. And again, the thing they liked the best was having access to

staff, to talk to them about specific decisions that came up. The role-playing didn't score as high as some things, but still complementary. The interviews, and the importance of having a session to come back and collect your thoughts about a month after the three intensive days, and not try and do the writing in that same session, I think was a strategy that the group liked.

We asked four open-ended questions, and we've given you all the responses to that in the handout, and I won't--they are on slides but I'm actually going to skip them, partly because the slides are unreadable, but also so we can have some discussion.

DR. NEREM: Your time is about up.

DR. FEIGAL: Oh, is my timer going to go off? Okay.

So what are the next steps for us? One of the things that we did is, we established a CDRH Recommendations Committee, a committee to go over the Science Review Board recommendations and to make recommendations to the senior management and

the team that's developing and continuing to develop and implement the strategic plan, to really look at how we incorporate these recommendations into our other activities. And let me just acknowledge this group.

You will notice this group has, if you know our alphabet soup, which Bob and Alexa now have memorized, there is someone from all six of our offices. And because of the emphasis on quality and quality systems and peer review, we actually have quality systems experts because it's one of the things we inspect industry on, and we've actually asked them to take a look at us. One of our one-liner goals for ourselves sometimes is, "Gee, we'd like to be good enough to pass an FDA inspection."

We have scheduled a go-away for our division directors in December, and one of the real focuses there is going to be to particularly look at the human resource issues and the kinds of things that we can do already at a local level. And the focus of that day will really be to ask the

division directors, what can I do in my own shop now? If I were to say things that I could take and implement all by myself for the family of staff that I'm responsible for, what is it that I think I can accomplish for the next year? And then, of course, they can also lean on the rest of us, to let us know what kinds of resources and support are needed for that.

And as of this afternoon, we're posting this report. We really welcome the report, and we even had a preview, you know, because Bob was kind enough to come up and present this to the office directors two weeks ago. We knew what we were posting. And we have arranged to have videotapes of your presentation and this afternoon's comments replayed in the Center, and will be available for people. What we will ask the CDRH Recommendations Committee to do is to prioritize the recommendations, to identify which are things that are short-term and which of them are longer term goals, as I mentioned, to make these recommendations on how to merge into the strategic

plan.

I think one of the themes that you developed, I would just like to sort of comment a little bit about at a high level, sort of how I see the strategy. And I think in some ways it begins to change the way that we think about doing the business, even though many of the elements are there, and many of the things that you ask us to do are not things that we don't do at all, but we do them as you describe, in groups that sort of work more or less autonomously. They actually pull together quite nicely in a crisis, and I think you saw evidence of that when we presented some of the cases, and there is quite a bit of interaction, and when they need to get together, they know, the staff knows how to do that.

But I think one of the things that your recommendations make clear is that we would be more effective and much more powerful as a scientific group if we could knit it all together. And one of the issues is how do we deal with new technology. We've had several on the horizon. One that gets

mentioned sometimes, very often, is the revolution that's going to occur for genomics, and our part of that will at least be diagnostic testing. Over 1,000 diagnostic tests for genetic diseases are under investigation and are available now that weren't available five years ago, so it's really an area that is exploding. And ask us if we could do 1,000 PMAs in a year.

Well, part of the process, this is sort of--you know, I think what your challenge to us would be is to get down to the nitty gritty to do this, is to have a process that scans the horizon. We have done that, and some of the responsibility for that actually has been OST, to identify the kinds of technologies that are coming along.

One of the first things industry always wants to know from us, though, is what's the regulatory path, and that's sort of one of the complaints often, is that there is this down time while they try and figure out how they're going to get this product to market, and whose product is it? It is going to be Kathy? Is it going to be

us? Heaven forbid, both of us? And they probably haven't come up with four-Center combinations yet, but I think we've had a couple of three-Center combinations.

And this is the time, shortly after that, to begin identifying the external expertise and using external expertise. That is the best way to actually build that expertise into our own staff and our own workings, at a time before we have much action. So while I mentioned that we actually are at the point where we have work for geneticists on the staff, but for a long time it was on the horizon, it was coming, but there weren't any products, people weren't talking to us.

But I think this is something we often don't do, and we haven't done aggressively, is to really identify how do we find the external experts and really build them and make them part of the team, and then at a point when a product area becomes busy and begins to pan out, to build internal capacity and develop our own staff. Some of that initially would logically be retraining of

people that have done similar types of things. That is how we have had to deal with many of the issues of bioterrorism, is to look at the skills mix of existing staff who really weren't doing bioterrorism before and say, how do we now turn you in this way?

And then, finally, I think we need to begin to consolidate a team that works across the whole life cycle. We're often actually not too bad at taking a new technology and getting it to market. But if it's a brand new technology, we may not have thought yet about the human factors, about the post-marketing problems, about how rapidly the generations of that product are going to change, what the issues are in terms of risk communication and communication about the products. And I think that we are beginning to pull together a conceptualization of sort of how we need to do business in a way that explicitly takes on new technology, and doesn't just put us in the reactive mode of waiting to see what comes in and what gets filed.

As you know, we have presented before in a brief form the theme areas that we developed about 15 months ago for the strategic plan, and one of the good questions you can always ask of strategic goal areas is whether they serve you when you get a new challenge and have something that you need to do. And actually I think that many if not most of your recommendations fit well into groups we have organized to work on these issues.

The semi-porous silo issue is a quote I liked enough that the staff have already heard me repeat it as the characterization of the Center. It's something that we are aware of, as we look at the need to work the Total Product Life Cycle, and are aware of the fact we don't quite do it yet. We do it with handoffs now, more like a relay team than a team all pulling together.

The Magnet for Excellence to really develop our staff and human resources is an issue not just for recruiting new people but developing the very talented and dedicated people that we have.

Knowledge management, and where these two things meet or how to develop expertise databases, there are some very interesting tools and technologies out there now that may make this more helpful.

And then the final area is meaningful metrics, which is that we really want to be able to measure the impact that we have when we take something on, not just do it because we think it would be a good idea, but actually to be able to say, what is it that we're hoping accomplish with this? So, for example, if we have a mentoring program, it's good to have mentoring programs, people in them like being in them, but I would like to then ask the question a step further: What are we trying to accomplish with that, and how do we know if we have a successful mentoring program? In my mind, one of the things it needs to help us do is transfer some of that institutional knowledge and help us with succession planning, because a lot of our retirement will be with our more senior people in the Center.

So, you know, in short I think the other way to come back and ask whether or not our efforts to do the internal review and the advice we got with you really stayed focused on the core thing about the Center, which is our mission, which is really pretty straightforward: promote and protect the health of the public; safe and effective medical devices; safe radiological health products.

And I think both of us are actually on that, on that mark. I think that there are things that, as you said in one of your slides, were not things we would accomplish overnight. There actually I think are some things that we should be able to start on very quickly, and I think one of the things that we need to do is to really identify where we want to go and what we think the challenges will be to do that.

And we need to do that without saying, "Well, we'll do it if we get a good budget," or "We'll do it if we get these new things funded," or whatever. These are things that are so fundamental to the way we do business, we have to take a look

at our resources and say, "Hey, we've got 1,000 people in Rockville, 1,400 people nationwide, a budget of about \$140 million. We ought to be able to do something with that."

Let me just close with a thank-you for all your time. I hope you will expect a progress report from time to time, and we will--we are starting on this activity already. So thanks very much.

CHAIRMAN LANGER: So, comments or questions for David?

DR. NEREM: Alexa, did you want to make any comments?

DR. CANADY: I just think that, sitting here this morning, many of the issues that we discussed this morning are directly applicable here. So I think it--but the key issue I see is the need to support with education and training the existing staff, as well as the new staff. That, like in most places, loses out to number counting and just budget deteriorations, and I think it is critical in a time of technological advance like

we're in now.

CHAIRMAN LANGER: Comments from people on the Science Board, or from the audience?

DR. KANTOR: Can I make a comment? I am Gideon Kantor, Adjunct Associate Professor of Biomedical Engineering, Catholic University, and as I said before, until '95 part of FDA.

These are excellent reports, but I would like to draw attention to a point that I think was part of the report but maybe not as emphasized as I like to do it, and that is linkages. Linkages are extremely important. Now, for that purpose I have mentioned briefly before that you need a meta search engine, and what I'm talking about is that the different offices are looked at from the keyword point of view. What are the keywords that identify the differences in their subdivisions? Then all the computer does is link those keywords together.

Now, let me give you an example. For example, medical device panels, they are the categories of medical devices in terms of clinical

applications. At the Office of Science and Technology there are breakdowns in terms of science and technology. Obviously the medical devices contain some of the components of the Office of Science and Technology, so that's just one example.

For example, you have an implanted defibrillator. You are concerned about particular technical issues, say interpretation of signals, say safety of equipment. If you have these keywords, you could easily link them.

So what I'm proposing is the following: that each office and subdivision looks for some keywords that are common to other entities of the organization, and then when you have established these linkages, establish a panel of experts that validates these linkages.

I know it is a new idea, and a lot of people are opposed to it for many reasons. I think many of them are good reasons, but when we look into the 21st century with the information explosion, we need to put some order in the complexity that surrounds us. And just looking

individually at issues is a very good idea, but it is beyond sometimes our capability of our brain, that which decision scope has not been increased.

So I very strongly believe in this, and I hope that people tell me if they do not believe in it, because at least I can learn from these. Thank you very much.

MR. BENSON: I'm Jim Benson with Avimed, and I think this is not on but that's probably okay if you can hear me.

DR. NEREM: You have to lower yourself, Jim.

MR. BENSON: I have to lower myself? I thought I was raising myself when I came to this meeting.

[Laughter.]

Just for the record, I went to Georgia Tech and the University of Maryland.

[Laughter.]

Also, I didn't know whether to stand up when David asked for people in the Center to stand. I was a little torn there.

I want to just say a couple of things. One is compliments to this Board for establishing this look, and specifically to the subcommittee which Bob chaired, and also very much to the center, to David and the folks in the Center, because from my own experience at FDA, introspection, organizational introspection isn't always a fun process, and so I think everybody should be complimented for that.

A couple of specific comments, if I may. One, I think the emphasis on looking at new technology, the exploding, I think that's a critical step. The concept of OST looking at, paying maybe perhaps more attention to new technology, perhaps along with that letting go some of the ongoing projects, I think can be a challenge and a very exciting one. I think looking to the outside for help for the existing expertise in the Center is terrific. I think that budget is a problem there, but I think there are ways that the budget can get increased, as well as under existing budgets to be able to enhance that.

I noticed in Bob's report, you included industry, scientists in industry as part of that. I would encourage David to include that in his outreach slide. And I'm not nit-picking here, I just think the concept is important.

If the agency wants, for example, to really take a look at new technology and some of the problems associated with that, probably if you look to the industry as well as to academia and other institutions, that combination I think can be enormously helpful, and we really need to figure out a way to accomplish that. Thank you.

CHAIRMAN LANGER: Other comments? Anybody on the Science Board, any questions?

Well, then we are supposed to decide whether we want to accept this report, I guess.

DR. FENNEMA: I would move acceptance of the report.

DR. PRINCIPE: Second.

CHAIRMAN LANGER: So why don't we vote? It has been moved and seconded, so we're going to vote on it.

DR. SCHWETZ: I did have a question, but Bob and Alexa, I want to thank you very much for all of the work that you obviously put in, and you took this very seriously. You were innovative in responding to what David came up with as an innovative approach. So on behalf of the agency, if we have a good review of a component, it helps the agency broadly. So I thank you for all of the work you did as well as the rest of your team, and we will get thanks out to the rest of the team as well.

My question is this: These reviews were not meant to be the end, they were meant to be the beginning of a process. Having taken this innovative approach of taking one product line from top to bottom, as opposed to the horizontal approach that we've taken in other Centers, what do you recommend as a follow-up? Do we go in greater depth to this, or do we go horizontal, or do we pick another piece and go vertical?

DR. NEREM: My own view, and Alexa may wish to comment also, but I think, I really believe

that the most important part of what happened was the internal review that took place. And I think that somehow needs to be brought into, if you wish, business as usual. It's part of one of our recommendations of taking a reflective look, not to criticize people for decisions that may or may not have been made but simply to look at what has been done and use that as a learning experience so as to do things better in the future.

And certainly there are other areas of CDRH where the report card might not be exactly the same as in the electrostimulation device area, so it's important to look at these other areas. I don't think that requires an external team to come in. I think that's something that can be built into a regular internal review process, and maybe each year look at a part of what's going on.

DR. CANADY: I really agree with everything Bob said. I would add one piece. I think that it was valuable for the members of the CDRH to have an opportunity to talk without management present and make arguments, and that you

can't really get with the internal review process, but I agree that the internal review process was critical. We could never have gotten this far. We would have spent a lot more time trying to understand things if we did not have the internal review process.

DR. SCHWETZ: I just want to give credit where credit is due. Dr. Fennema was the one who had the idea that this was an essential and critical part of the review process, and we have used it since he provided leadership in a review team of CFSAN. And when that was brought back to the Science Board, it was approved as an institutionalized process.

So I have always felt that the internal review is the most beneficial part of any of these reviews, and what you get from the external reviewers is additive to that. But the reality is getting your own people internally to recognize what they're doing and what they haven't done and to deal with it. And I would say that we are going to continue to have these internal reviews as

we go through the rest of the Centers, and I would encourage that, to the extent that they are useful internally in the absence of an external review, that we would look at that as well.

So, Owen, thanks for an idea that has become very beneficial to us.

DR. NEREM: But in addition to this being used as part of the Science Board review structure, it also could be built into the business as usual of the Center.

CHAIRMAN LANGER: One question I had--go ahead.

DR. FEIGAL: I was just going to comment on some of the processes that we plan to take forward. We actually appreciated the suggestion to actually now do a review of OST. We think actually this larger view now actually gives a context to look at the research efforts both in OST and in some of the other areas like epidemiology where we have specific research projects, and we can actually look at them.

Another effort which has been going on,

and actually has an external component as well, has been for us to look at the Radiological Health Program, since this Center is the merger of two different programs with different authorities and different laws, and we didn't really try and do the Rad Health Program, except there was some overlap. And so those are two activities that will be extensions or continuations of that, in addition to tackling some of the explicit issues from this report.

The internal review was definitely something that we did get from Dr. Fennema. We actually hadn't initially planned to do it. We had an internal group preparing for the external review, but we actually pulled a separate team together that was more senior than that group and asked them to actually prepare the internal review report, and it was the right decision to do that.

CHAIRMAN LANGER: Any other comments or--
yes?

DR. ROY: Suva Roy, Otsuka Maryland
Research Institute. I have never worked at the

CDRH, but I have worked in the Center for Devices. One of the things I would like to see perhaps this meeting address, and that is the qualification and experience requirements for reviewers. Many of the job descriptions, at least I can speak from the Center for Devices, many of the job descriptions were written 30 years ago and it has really not changed, or the experience or qualification requirements. But if those things are not updated, the Centers may not be able to attract or retain the best possible people. So you can retrain people, but it's like somebody said, you cannot buy a Volkswagen Beetle and expect to run it like a Porsche. You have to have something underneath to work from. Thank you.

CHAIRMAN LANGER: Bob?

DR. NEREM: Yes. On that comment, I mean, I think as part of really doing an in depth look at the kind of staffing needed five years from now and strategic recruiting, you really have to look at how different positions are defined.

The other thing I wanted to comment on was

Jim Benson's comment. I mean, we specifically included industry, and I noted it was left out of your slide, David. I realize that industry on the one hand is what's being regulated. On the other hand, for certain technologies, the expertise is actually out there in the industry, and if you're going to learn about those technologies you have to take advantage of that, and you have to somehow walk that balancing act.

CHAIRMAN LANGER: Okay. Well, thank you very much. I think that's an excellent review.

The next thing is emerging issues and FDA's oversight of clinical research, and David Lepay will discuss that.

DR. LEPAY: I'm going to change the focus of attention a little bit here. What we're going to talk about for the next 20, 25 minutes are clinical trials, the conduct of clinical trials and the oversight of clinical trials, and some of the events that are taking place here within the agency and in our interactions with the department.

I think first and foremost, though, when

we start off here we have to give ourselves a very large round of applause for the progress that has been made over maybe the past 25, 26 years in the area of clinical research. If you look back, it really is very much since the mid-'70s that certainly most of the infrastructure that exists today for the oversight of clinical trials, for IRBs, has been put in place.

The Belmont Report, which specified many of the ethical underpinnings of our current models, is less than 25 years old. The true implementation of evidence-based decision-making at the agency probably has taken place within the last 25 years, even though it was put in place with the Kefauver-Harris amendments to the FD&C Act. And even our standards for research conduct, 10 years ago we hadn't really defined what good clinical practice was in the agency, and it was only when we began moving internationally into harmonization that we began to move forward in that direction as well.

And, similarly, we have seen a lot of attention to quality improvement, quality assurance

systems in this period of time, and ultimately a very significant improvement in the quality of clinical research as FDA has viewed this in the course of our own oversight, in the course of our own inspection system.

In 1977, the first year that we began looking at clinical investigators and clinical trials, we were seeing certainly quite a number of problems, and the percentage at least--granted, we didn't do very many inspections back in the '70s-- the percentage of what we are seeing now in terms of major problems, the red there on the graph, is down on the order of about 2 to 3 percent where FDA has to come in and take official action in clinical trials. But that is a percentage change.

We certainly know that the clinical trial landscape has changed markedly over the past 25, 27 years. We may see fewer percentage problems, but we know there are more sites, there are more special investigators. We know that from the standpoint of trying to get good clinical data on populations that will be using our products, we