DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Tuesday, October 19, 2004

8:30 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

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Hilda F. Scharen, M.S., Executive Secretary

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Nozer Singpurwalla, Ph.D.
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Qian Li, Ph.D.
Robert Lionberger, Ph.D.
Robert O'Neill, Ph.D.
Amy Rosenberg, M.D.
John Simmons, Ph.D.
Keith Webber, Ph.D.
Helen Winkle
Lawrence Yu, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

CHAIRMAN KIBBE: Ladies and gentlemen--welcome. I want to take a little page from the coach at the New York Times, who says that a meeting that starts that eight o'clock actually starts at five minutes before. And to get us rolling in about 30 seconds, ahead of time.

Do we know--

[Comment off mike.]

--he'll be here tomorrow. All right. So--Dr. Amidon, my co-pilot here, will be here tomorrow.

I'd like to call you all to order for my last go-round as Chairman of this August body. And the first order of business, of course, is to read about all of our conflicts.

Conflict of Interest Statement

MS. SCHAREN: Good morning.

The following announcement addresses the issue of conflict of interest with respect to this meeting, and is made a part of the record to

preclude even the appearance of such.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability, and there are no products being approved. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees have been screened for their financial interests as they may apply to the general topics at hand.

To determine if any conflict of interest existed, the Agency has reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration has granted general matters waivers to the special government employees participating in the meeting who require waiver under Title 18, United States Code Section 208.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30

of the Parklawn Building.

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they may apply to each member, consultant and guest speaker. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclosed that Paul Fackler and Mr. Gerald Migliaccio are participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry.

Dr. Fackler's and Mr. Migliaccio's role on this committee is to represent industry interest in general, and not any one particular company. Dr. Fackler is employed by Teva Pharmaceuticals, U.S.A., and Mr. Migliaccio is employed by Pfizer, Incorporated.

In the event that the discussions involve

any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

CHAIRMAN KIBBE: Thank you.

And now we'll hear from the Director of the Office of Pharmaceutical Sciences, Ms. Helen Winkler.

Introduction to Meeting

MS. WINKLE: Good morning, everyone.

All right, I want to welcome everybody this morning to the Advisory Committee for Pharmaceutical Science. This is, I think, a very important meeting, and I"m really looking forward to the discussion. But before we get there, I want to welcome all of the members. We have one new

prospective member, Carol Gloff--Dr. Gloff--has joined us. And we have two other prospective members who we're having a little complication with in getting on board. So we're working on that.

We also will have a number of SGE's here today; Dr. Boehlert, Dr. Amidon and several others who are going to participate with us in a number of things. So I want to welcome everybody.

I also want to thank Dr. Kibbe. This is his last time as Chair. It will break all of our hearts to see Dr. Kibbe go out of this position. He has been very, very enthusiastic as the Chair of this committee, and I think all of us have enjoyed working with him. But he's not to go very far. We've already told him that we anticipate him coming back to a number of meetings and helping us with some of the discussion in the future. So we really want to, again, thank him for all he's done.

Dr. Cooney--Charles Cooney--has agreed to be the chair of the committee for the next two years. Unfortunately, Dr. Cooney couldn't be here--after he accepted, he couldn't be here today.

But he will be here at the next meeting. So--he's been very gracious to accept this position. He and I have talked at length about some of the issues we want to cover on the Advisory Committee, and he's very enthusiastic about moving ahead for the future of the committee.

The agenda for the meeting today: there's a number of things we want to take up. I'm going to talk a little bit about next year--2005 being, I guess, this fiscal year--and some of the things that we plan to take up with the Advisory Committee, where we're going in OPS, just to give the committee a little feel about some of the things that we're looking at.

I also want to give a quick--and I mean a quick--update of the cGMP Initiative for the 21st Century. We're also going to have an update on a number of the subcommittee and working groups. Dr. Boehlert is going to talk about the Manufacturing Subcommittee meeting that we had several months back. It was a very, very--we accomplished a lot, I think. It was a very good meeting. And Judy can

fill us in on some of the highlights of that meeting. Also Bob O'Neill is going to talk about the Working Group with IPAC RS, and some of the accomplishments--or the focus that we've had in that Working Group.

We're also going to talk about the Critical Path Initiative. And I think this is a really important discussion that we can have with the committee today. Critical Path is, of course, one of the main initiatives in the agency now, and what we would like to talk about with the committee is give you some idea of our thoughts, as far as Critical Path; some of the things that we're doing in the Critical Path Initiative, in the office of Pharmaceutical Science in the various product areas, and get some input from you as to what direction we need to go; if there's other things we need to be thinking about; and if there's other types of topics that we need to be taking up, we'd like to do that.

Dr. Woodcock talked about the Critical Path Initiative when she introduced it, saying that

FDA was really in the best position to identify those areas, or those gaps, in drug development, and to work with others--collaborate--on how we could get the data necessary to fill those gaps.

So this is really what we're looking for doing under the Critical Path Initiative. And we need to be certain that we are identifying the gaps correctly, and that we are able to do the types of research that needs to be done to fill those gaps. Of course we can't do everything, so I think some of what we want to talk about and think about, too, is how we can prioritize some of that research.

Tomorrow, we're going to talk about manufacturing, and moving toward the desired state. As I said, we had a very productive meeting of the Manufacturing Subcommittee. A number of things were identified at that meeting that we need to discuss further; that we needed to look at and determine how we're going to do it. A number of questions that we need to answer--and we're looking at possibly having a subgroup to do some of that--a fact-finding group. So Judy will talk to that.

But there are a number of things, too, that we want to talk about with the committee today; a number of--the gaps that we recognize that we have in OPS and the agency, in moving toward that desired state.

So several of us are going to talk about those gaps. We're going to talk about the organizational gaps, the science gaps, and the policy gaps--all of which are important if we in the agency are going to be prepared as the manufacturers and others move toward that desired state.

So I think that will be a really interesting issue, and I think there are a number of things that the committee can help us with in identifying how best to address these answers and to address the gaps.

We also have a number of bio-equivalence issues that we want to discuss. We want to continue the conversation from the last Advisory Committee we had on bio-equivalence. And Dr. Yu and some of his staff are going to talk about some

recommendations from that. And we're also going to bring up a new topic on gastroenterology drugs.

So--moving on to OPS in 2005. I think 2004, we had an extremely busy year, mainly focused on the GMP Initiative, and all of the aspects of that initiative--especially the areas concerning manufacturing science and how wee were going to really address those issues and concerns, and how we were going to incorporate those into the regulatory framework.

As we move into 2005, I think we still have a lot of issues that we have to handle under Pharmaceutical Quality Initiative. We've already said that that's going to be some of what we take up with the Advisory Committee today. But we really need to pursue those next steps. In doing that, though, we also need to be looking at continuing to streamline the review processes. We continue to get more and more products in for review, and there's got to be some way to offset that increasing workload. And streamlining the review processes seems to be--we're moving in that

direction, and it seems to be the answer to handling some of the enormous workloads that we have.

Also, we need to incorporate best practices. We've added the Office of Biotech Products in the last year. They joined us in October of 2003, and they have a lot of practices in their review that I think can be very helpful as we move forward in looking at ways to improve--both in out office of New Drug Chemistry, and our Office of Generic Drugs.

So we're going to be looking at incorporating best practices across the entire organization.

Supporting the Critical Path Initiative--I've already brought this up. It's a very important part of where we're going. I think much of our research is going to be done there, and I think we're talking about much more than laboratory research. I think there's a number of activities that we hope to take on in 2005 where we're looking at improving on how we do the

regulation, and in actually working through the Critical Path Initiative to get some of this done. So we'll talk more about that as we get into Critical Path and some of those projects that we're looking at doing.

We're looking at further integrating the whole Office of Biotech products. There are still some things that need to be accomplished there. I think there are still a number of questions that the Advisory Committee can be very helpful to in answering. So you will hear more about this in the next fiscal year.

And, last of all, I think there still continues to be a number of regulatory on follow-on proteins, as well as a number of general scientific issues that we'll want to discuss with the committee.

So I think we have a lot on our plate during the year, and I look forward to working closely with the Advisory Committee in the next fiscal year to help us identify some of the--other things that we need to look at, as well as help us

with the issues that we already have identified ourselves.

Okay. As I said, I'm going to talk real quickly about the CGMP Initiative for the 21st Century. I think most of you all have probably read the background material, which included the report. We've actually come to the end of the first two years of the initiative. And I"d like to emphasize: I don't think that's the end of the initiative. I think it's just the beginning. I think that the initiative helped us identify a number of things that we need to be looking at in review, that we need to be looking at in inspection. We still have a lot of changes to make. I think we've made a lot of progress--and I'll talk a little bit about some of that progress. But I think we've got a lot more that we have to focus on.

So that was only, in my mind, the first step.

But I thought it would be helpful just to step back real quickly and look at what the goals

of the initiative were. Because I think you can't really appreciate the accomplishments without really understanding what the goals were.

So there were basically six major goals. The first one was to incorporate the most up-to-date concepts of risk management and quality systems approaches; secondly, was to encourage the latest scientific advances in pharmaceutical manufacturing and technology, ensure submission review program and the inspection program operating in a coordinated in synergistic manner; apply regulation and manufacturing standards consistently; encourage innovation in the pharmaceutical manufacturing sector; and use FDA resources most effectively and efficiently to address the most significant health risks.

And you can see, when you look back at these initiatives, the role OPS has had to play in all of these goals. I think they're very important, not only to the agency, but important to us at OPS, and important to the industry and others involved in the manufacturing of pharmaceutical

goods.

So, quickly, through the accomplishments--again, you can read the report. You'll get a lot more out of the report. But I just want to emphasize that there was an awful lot done in the last two years; a lot that will affect how we move forward in the future, in the 21st century. So I wanted to highlight those.

The first thing was Part 11. We did a last in the last two years to clarify the scope and application of Part 11. There were quite a few questions; quite a bit of complication in implementing Part 11. And I think we've moved forward in trying to eliminate some of that complexity and complication. We issued two guidances during the two-year period that have helped in that clarification.

Technical Dispute Resolution Process--this was also a very important part of the initiative. And it really has had a very positive effect, I think, on the industry, and a positive effect on how the field has dealt with inspections and has

increased the time and effort that the inspectors are putting into the inspections, and the time and effort that they're spending with industry when they go in and do these inspections. And it has really been the basis of much discussion in the inspection process. And the outcome--we have not had any technical disputes. We have a very good process--as I said, the process has sort of set the framework for opening up the discussion. And so I think that it has had a really positive effect. I'm actually a co-chair of that group. I kept waiting for disputes. I thought we were just going to have tons of them. We have a pilot program, and I thought in the 12 months of the pilot we'd be able to figure out how best to run the program. But not having any disputes, we haven't learned a whole lot of lessons.

But, again, it's had its very positive effects. So I think that it has really been useful under the initiative.

The GMP warning letters--this was an issue that was handled very early on. And we

accomplished the goals that we wanted under this particular working group of the initiative; and that's that warning letters now are reviewed by the Center to ensure--in the Center before they go out to the companies--to ensure that they have adequate scientific input. Many of the warning letters that went out in the past were not reviewed to make sure that the issues were scientifically sound. So that has changed now. And I think that's had a very positive effect.

International collaboration--I won't go into that, but we have spent a lot of effort in ICH, and Q8, Q9, and hope to do a lot in Q10. And also one of the things we are planning on doing is getting more involved with PICS, which is looking at inspections on a worldwide basis.

Facilitating innovation--including doing standards and policies--we were very fortunate to put out a number of different guidances under this part of the initiative; the aseptic processing guidance--which industry is very familiar with. They've been waiting for this guidance for a long

time. And I think it addresses many of the questions that have been out there in industry's mind. So I think it's a very, very positive part of the initiative that we were able to accomplish.

The next guidance that was put out--I think many of the people--in fact, everyone on the Advisory Committee is very familiar with this guidance, because we did have a subcommittee on the PAT--the Process Analytical Technologies--under the subcommittee, and we were able to put, under Dr. Hussain and others in the group, we were able to put out a guidance to industry which has had an extreme effect, I think, on how industry and others are looking at manufacturing in the future. I think it's been probably one of the best parts of the whole initiative. It really has promoted the two--the team approach to doing work; working on standards. We've worked with ASTM under E55. And I think, all in all, this has been an extremely successful initiative under the GMP initiative.

The last guidance that we've had, that was comparability protocol. That guidance is still in

limbo. We're trying to make sure that before we issue the guidance that we're not increasing the regulatory burden--which I think many of us felt when we read the original draft guidance. So we're busily working on that to make sure that what we come out of is very beneficial to industry and to FDA, and that we don't put any additional resource requirements on either part of the regulatory system.

Manufacturing science--the desired state under !8 of ICH has become a very important aspect of where we're driving to. And, of course, we're going to talk to that tomorrow morning; continuous improvement and reduction of variability have been an important part of manufacturing science, and areas that we need to explore more in the future, and assure that we can accomplish that, especially being able to open up in the agency and allow more continuous improvement for manufacturers.

Product specialists--this includes enhancing the interactions between the field and the review. We're looking at a team approach, in

having our reviewers all out on inspections. And we're looking at best practices from both the PAT team and Team Biologics. I think there's a lot of best practices there that we can incorporate in out thinking in the future on how we handle review and inspection.

Integration of approval and inspection--this is more of that. We have developed the pharmaceutical inspectorate, and we're looking also at changes in pre-market approval program.

Quality management systems--there's a number of things that we've worked on here. They take a number of directions. We've developed a standard quality systems framework; a quality systems guidance. We've worked on GMP harmonization, analysis process validation, and good guidance practices--none of which are going to go into in detail, but I think all very beneficial to helping us in the future in the 21st century.

Risk management--risk management, I had thought--we did introduce a site-selection model

for inspection under this part of the initiative. I believe there's a number of other things that we, especially in Review, need to focus on as far as risk management, and have a much better idea of what the risk of products are, and how we're going to mitigate those risks. And I think this is something that we will bring up in the future at the committee.

Team Biologics was to look at a number of initiatives that were already underway, and adopt a quality systems approach.

And last of all was the evaluation of the initiative, which hasn't been completed yet, but it's a very important part of what we've done.

So that, in a nutshell--I mean, that's a lot of effort, obviously, that we've done. And if you, again, will read the report I think you'll get a much better feel. But I felt like, since we've talked about it so much during the last few years, that it was very important to sort of wrap up what has happened in the last two years with this committee.

So that's all I have to talk today. I'm going to give it back to Art, and I look forward to very lively discussion on a number of these issues, and look forward to working with you for the next two days.

Thank you.

CHAIRMAN KIBBE: Thank you, Helen.

We now have a report from the chair of one of the subcommittees--the Manufacturing Subcommittee.

Judy?

Subcommittee Reports

Manufacturing Subcommittee

DR. BOEHLERT: Good morning, ladies and gentlemen. Before I just get started here--I tried pressing down, and--aha. I need an SOP for how to operate the slides.

[Slide.]

It's a pleasure for me to be here this morning to update you on the Manufacturing Subcommittee. We met in July. And I think you'll find that a lot of the topics we discussed tie in

very well with what Helen was talking about this morning, and also with some of the topics that are going to be on your agenda.

[Slide.]

We met for two days in July. Just a brief overview of the topics that we discussed: quality by design--we've heard that this morning; introduction to Bayesian approaches--and we'll talk just a little bit about that; research and training needs--the industrialization dimension of the Critical Path Initiative--another topic we heard about this morning; manufacturing science and quality by design as a basis of risk-based CMC review; and risk-based CMC review paradigm.

[Slide.]

On the 21st: introduction to pharmaceutical industry practices research study; a pilot model for prioritizing selection of manufacturing sites for GMP inspection; cGMPs for the production of Phase I INDs; and applying manufacturing science and knowledge, regulatory horizons.

What I'm going to do is just go over, briefly, some of the topics that were discussed, and also the comments that were made by committee members.

[Slide.]

Quality by design: topic updates. This addressed three guidances that should be coming out of ICH. The first of ICH Q8, which is a guidance on pharmaceutical development section of the Common Technical Document. It's going to describe baseline expectations and optional information; requires FDA and industry to think differently. Industry needs to be more forthcoming with information in their submissions, and FDA needs to look at the review process; focuses on process understanding and predictive ability. And if you really understand your process, you'll gain regulatory flexibility. It's a framework for continuous improvement. And Step 2 is expected in November this year. That means it will be out for public review and comment.

[Slide.]

ICH Q9 is quality risk management. It looks at risk identification--should link back to the potential risk to the patient, because, after all, that's what's important; risk assessment--what can go wrong? What is the likelihood? What are the consequences?

Risk control--options for mitigating, reducing and controlling risks; risk communication--between decision makers and other shareholders. And this may also reach step two in November of this year, although that was a bit questionable.

[Slide.]

And then we're going to talk about quality systems needed to recognize the potential of !8 and Q9. And this is ICH Q10: monitor and evaluate processes with feedback groups in a manner to identify trends and demonstrate control or the need for action; manage and rectify undesirable occurrences; handle improvements; management, implement and monitor change.

This is currently on hold, not because

it's not a good topic, but primarily because all the resources that would address Q10 are tied up with Q8 and Q9.

[Slide.]

We also talked about the ASTM E55 Committee. And Helen mentioned that this morning. Their involved in the development of standards for PAT. And the important things here are consensus standards, with input from industry, academia and regulators. There's an established process, with an umbrella set of rules. And ASTM is recognized worldwide.

They have three functional subcommittees on management, implementation and practices and terminology. But one of the concerns expressed by the committees is are they going to duplicate other initiatives. There area lot of people right now working on PAT initiatives, and are they going to duplicate some of that. So we need to make sure that everybody gets on the same page.

[Slide.]

All right. Now, this topic I'm going to

be reluctant to say a whole lot about, but we had an introduction to Bayesian approaches. Dr. Nozer Singpurwalla was kind enough to give us an introduction to the topic. So, Nozer, I apologize if I mis-speak when I summarize--[laughs].

You know--so it's with fear and trepidation--he's threatened us a quiz--

DR. SINGPURWALLA: You've already done it.

DR. BOEHLERT: Yes, I know. [Laughs.] That's what I was afraid of. But I didn't think I could leave it out, or you'd get after me then, too.

Okay--Reliability for the Analysis of Risk." Reliability--the quantification of uncertainty. And I'm just going to say a few words here: utility--costs and rewards that occur as a consequence of any chosen decision. These are the things that Nozer talked to us about--risk analysis--process assessing reliabilities and utilities, including an identification of consequences. We talked about scales for measuring uncertainty--for example, probability.

[Slide.]

Now this is a quote, so I have to be careful here. "When the quantification of uncertainty is solely based on probability and its calculous, the inference is said to be Bayesian." I am not a statistician, so I'm certainly not a Bayesian statistician. And then there is discussion of use of Bayesian approaches for ICH Q8, Q9, Q10 and the use of prior information.

[Slide.]

Industrialization--dimension, the Critical Path Initiative. We heard about that this morning. We'll hear about it in the next two days: examining innovational stagnation. Everybody needs to take a look at what we've been doing in the past and get things moving forward in a new environment, with new technologies.

Critical path--has been inadequate attention in areas of new or more efficient methodologies and development research.

Industrialization--goes from the physical design of prototype up to commercial mass

production. And Education and research infrastructure needs improvement. And this education and research applies to industry; the education also applies to the agency. We all need to learn how to go forward in the new environment.

[Slide.]

FDA has a strong interest in computational methodologies to support chemistry and manufacturing control submissions. They're putting together a chemometrics group. There's a new FDA research program focusing on industrialization dimension. And there's training needs. AS I mentioned before, particularly with the pharmaceutical inspectorate. That's started. There is an inspectorate now of trained investigators. There need to be more.

[Slide.]

Manufacturing science and quality by design--it's a basis for risk-based CMC review. Companies share product-process understanding with regulators. And this is a new paradigm, if you will, that companies will share more of the

information that they have available than they have in the past.

Specifications should be based on a mechanistic understanding of the process; there should be continuous improvement; and real time quality assurance. You shouldn't have to wait until the end of the process to know that your product is okay.

[Slide.]

Science perspective on manufacturing--define current and the desired state and the steps to go from here to there; define terms--and this is going to be important going forward--things like "manufacturing science," "manufacturing system," "manufacturing capability"--what do they really mean?

Real case studies will help. This came up time and again in the committee discussions. It's nice to talk about all these theoretical concepts, but give me a real case study that I can look at and see what it really means.

Testing is mostly non-value added.

Quality by design is the desired state.

[Slide.]

Risk-based CMC review--from the Office of New Drugs--should provide regulatory relief by incorporating science-based risk assessment; more product or process knowledge shared by the industry--and I've said this several times; more efficient science-based inspections; focus resources on critical issues; and specifications are based on a risk-based assessment.

[Slide.]

Quality assessment rather than a chemistry review--in the past it's been a strict chemistry review: go down the list and check off the boxes; conducted by inter--and I see some smiles on the parts of agency folks--conducted by interdisciplinary scientists--so it could be a team approach. It should be a risk-based assessment; focus on critical quality attributes and their relevance to safety and efficacy. They have to rely on the knowledge provided by applicants. If industry doesn't submit the information, the agency

has nothing to make their decisions on. And the comparability protocols are an important part of this review.

[Slide.]

Role of process capability in setting specifications will need to be addressed. Very often, those kinds of process controls that you have may have no clinical relevance. The knowledge base at the time of submission can be an issue, because very often you don't have that much information at the time you submit. It's a learning process as you go through early marketability and commercial production.

Specifications should not be used as a tool to control the manufacturing process. And we might need to expand the Quality Overall Summary going forward.

[Slide.]

AS I said before, the extent of product knowledge is key. Risk-based decisions should be based on supportive data. Voluntary--all of these new initiatives are voluntary. And that needs to

be made very clear to the industry. These are not requirements that everybody drop what they've been doing in the past and start over with new approaches--strictly voluntary.

Supplement need is based on the knowledge of the risk of the change. And there should be a clear rationale for the selection of specifications.

[Slide.]

Identify critical parameters for product manufacturing and stability; train FDA staff and regulated industry--this came up a number of times. We all need to learn what the other is doing; should give us--industry--greater flexibility in optimizing the process; should lessen the supplement burden, which is good for industry and good for the agency. And, once again, real examples would be an asset.

[Slide.]

In the Office of Generic Drugs--generic industry's focus is on producing a bioequivalent product. Often patent issues--to design around.

They may not have the flexibility as the new drug folks. Workload in OGD is a significant issue, and committee members made a number of comments on this when they heard how many submissions there are, and how far behind they are. We were impressed by the workload.

Provide advice to industry on improving quality of DMFs--those are "drug master files"--very important to the generic industry--also to the new drugs, but to a lesser extent.

[Slide.]

Desired state--include needed data in a filing; process and product design; identify critical attributes; identify process critical control points. And this is the difference from the past. Analyze data to produce meaningful summaries and scientific rationales; and reviewers assess the adequacy of the submission by asking the right questions.

[Slide.]

Okay--some additional committee comments

that came out of the Day One discussion: ICH and ASTM appear to be synergistic, but ICH needs to be very aware of the ASTM focus. There was some concern they might not be tied into what's going on there; some concern that FDA, internally, themselves, may be getting ahead of what's happening on an international basis. So they may be a little ahead of ICH Q8, Q9 and Q10. That's not necessarily a bad thing, by the way.

Need concrete examples--that came up time and time again; need to clearly demarcate "minimum" and optional information--you know, just what do you mean by "this is the minimum you need," and just what is "optional" information? And "optional" information comes in degrees. The more you make the more you know. So you may not have as much information at submission as you will down the road after you've been in commercial product for a number of months or years.

[Slide.]

Need to avoid implying there are two different quality concepts. We don't want to say

that products made in the conventional way---the way we've always done it--are different than products that may be made according to some new paradigms. Bring in new training programs--and Helen mentioned we're talking about forming a working group under the Manufacturing Subcommittee to address some of the issues, particularly case studies.

We need to find better terms than "minimal" and "optional;" and focus on process first, and then the tools that we're going to need.

[Slide.]

We had some reports on an FDA research project that's being done by Georgetown University and Washington University, and their goal is to identify attributes that impact inspection outcomes. They're compiling and linking FDA databases. They're looking at variables for product-process, facility, firm and FDA. Right now they're collecting data. CDER is just about completed, and CBER is ongoing--although by now it may be even further down the road. This was July.

[Slide.]

Focus--are cGMP violations related to managerial, organizational and technical practice? And then interviewing manufacturers. They have an internet-based questionnaire that went out in the fall of 2003. They're looking at U.S. and European manufacturers. And their data collection is near completion.

[Slide.]

There's concern with just looking at numbers of deviations or field alerts, particularly when investigation may have shown little cause for concern. You can put in a field alert and then find out later on that--oh--you know, we figured it out. It really wasn't a problem. So if you just look at numbers, you get those as well as the ones that are true issues.

Also it was pointed out that if you're a company with a very detailed SOP you have a much bigger chance for deviating from it than your company with a really poor SOP that sort of allows you to do anything, where you're hardly ever going

to deviate. But who's to say which one is better?

India and China are not include in the API manufacturers. And we saw this as a downside to that survey, because they are major manufacturers of APIs.

[Slide.]

We talked then about risk ranking and filtering, where risk ranking is a series of decisions to start to rank within a class or across classes. Tools may be customized for each application. And filters may be used to reflect resource limitations and/or program goals.

[Slide.]

There's a pilot risk-ranking model to prioritize sites for GMP inspections, using ICH Q9 concepts to define risk; Site Risk Potential--a new term for us--SRP--includes product, process and facility components.

Look at probability and severity components that make up harm; and look at other risk-ranking models, for example those used by EPA and USDA; and then using the CDER Recall database.

[Slide.]

Comments--from the committee--focusing on volume at a site may be misleading because, in fact, when you have a high volume your process may be better controlled than if you have small volume.

We need to also consider the risk of the loss of availability. If you're a single-source drug for a life-threatening condition perhaps that needs to come into the equation.

Look at "hard to fabricate" products, or products with difficulty controlling uniformity. Investigator consistency will be--and has been--an issue, but with the pharmaceutical inspectorate that should be better. And it was suggested by at least one member that maybe they should look at high personnel turnover in a plant, because that might be indicative of problems--although it was recognized that that might be hard information to come by.

[Slide.]

Committee members wanted to know if the sites are going to know how they are ranked. That

would be very useful information for management to know about. Right now self-inspections are a critical part of the quality system but the value of these would be diminished if that information were to become available to FDA. This has been a longstanding concern of industry. You know, you don't want to share your self-inspections because then they lose their value to you.

[Slide.]

Next talked about GMP guidance that's proposed for the production of Phase I drugs. CMC review to ensure the identify, strength, quality and purity of the investigational drugs as they relate to safety. This draft guidance is in process. It's a risk-based approach. No regular inspection program, but these Phase I drugs are looked at on a "for cause" basis.

I want to point out that it was noted during that discussion that for Phase 2 and Phase 3, those drugs still fall under the GMP regulations--21 C.F.R. 210 and 211.

[Slide.]

Also had an update on the PAT initiative. As Helen indicated, that guidance was recently finalized, in September. It should be expanded to cover biotech products. And, of course, it requires continued training of FDA staff.

[Slide.]

We also talked about--we had a full agenda--comparability protocol. We had an update on guidances, The goal is to provide regulatory relief for post approval changes. It requires a detailed plan describing a proposed change with tests and studies to be performed, analytical procedures to be used, and acceptance criteria to demonstrate the lack of adverse effect on product. Many comments have been received from the public. That was FDA's comment on this. We did not see those.

But the committee had comments, as well.

[Slide.]

Single use protocol has limited utility. It's more utility if you're going to have repetitive changes--if you're only going to do it

once it may not help. Specificity of the protocol may limit repetitive use. Just how much specificity is needed? And for a well-defined protocol, an annual report should be sufficient. That really will lessen the regulatory burden.

[Slide.]

Some general conclusions from our two days--and we've heard the first one several times--general principles are good, but case studies are needed to facilitate understanding. That came up time and time again. Case studies should cover all industries; for example, dosage form, API, pioneer and generic.

The committee expressed concern on what appears to be understaffing in OGD.

[Slide.]

Failure Mode &Effect Analysis can be linked with risk-based decision-making wherein the results feed into decision trees; training and education of both regulators and the industry in the new approaches is going to be key; historical inconsistency in regulator findings may limit the

utility of surveys. In the past, you know, not all investigators have investigated in the same manner, so it's difficult to compare results.

And that's the end of my presentation. I thank you for your attention, and would be happy to address any comments, now or later.

CHAIRMAN KIBBE: Are there any questions for Judy?

DR. SINGPURWALLA: I have some comments, but I probably would wait until all the presentations are over, and then make comments. Would that be acceptable?

CHAIRMAN KIBBE: Whichever way you want to do it, as long as it's within one of the two tails of the Bayesian distribution we're all right.

[Laughter.]

DR. SINGPURWALLA: You are confused, Mr. Chairman. [Laughs.]

CHAIRMAN KIBBE: On a regular basis.

[Laughter.]

You had a question?

DR. MORRIS: Actually, just one comment to

add to what you'd said, Judy, about the Georgetown study.

I think they had made sort of a plea that the reason that they hadn't been able to go to the Indian and Chinese manufacturers was strictly a resource issue. It wasn't that they had ignored that as an area of concern.

DR. BOEHLERT: Ken, thank you for that clarification.

CHAIRMAN KIBBE: Go ahead.

DR. KOCH: I guess, looking around on the schedule, I'm not sure if we're going to talk any about training. You mentioned it in several different ways: the continuation, the inclusion of industry, etcetera. But will that come up as a discussion topic at some point?

DR. HUSSAIN: Not in this meeting. I think we will eventually bring that back at some other meetings, though.

MS. WINKLE: Actually, when I talk about some of the organizational gaps I'm going to bring up training as part of that gap. So if you want to

comment then, it would be fine.

CHAIRMAN KIBBE: Anybody else?

DR. SINGPURWALLA: Well, maybe I'll speak now. I just--we--this is a question more to Ajaz--about case studies and specifics.

We've been through many sessions of the Manufacturing Subcommittee meetings. Has there been any concrete plan made to start seriously undertaking some case studies? And, if so, would you be kind enough to let me know?

DR. HUSSAIN: Yes. Dr. Boehlert's presentation to this committee--she's the chair of the subcommittee--and the decision was made to form a working group under that. And after this meeting we'll start populating that working group and create a working group under that committee to start addressing that.

In addition to that, I think we're also looking at other parallel tracks to create case studies. One such case study has just started to take shape, with Ken Morris, and then Purdue is working with our reviewers to actually develop a

case study also.

So we hope in the next several months we will have examples and case studies to outline the framework.

CHAIRMAN KIBBE: Anything else?

DR. SINGPURWALLA: Yeah. One other matter. After the subcommittee meeting, some minutes were released, and I had made some comments about the minutes. I did not receive an update of the minutes--update of the revision.

Has--is there any reason for that? Because the normal protocol--the normal protocol is you put out the minutes, people give comments on the minutes. You either incorporate those comments--and if you don't, you let us know why. And then you issue a final document of the minutes. And then the entire committee, or whoever it is, says "Yes, we go along with these minutes." And they should become a part of the record.

I was wondering if this was done, because I did not have access to that.

CHAIRMAN KIBBE: I think the final draft, or the final copy of the minutes is posted on the web page--FDA website--so that after the draft goes out to the members of the committee and the corrections come back in, they update to reflect the suggestions from each of the members, and then they post it.

So if you wanted to check the website you could see whether--you know, how well your suggestions were incorporated in the final minutes.

DR. BOEHLERT: I would just add, also, that I reviewed comments that were made to the minutes before I made this presentation, and I tried to make sure that they were all incorporated in what I said today.

DR. SINGPURWALLA: I thought so.

DR. BOEHLERT: If they were not well reflected in the minutes, they should have been reflected in my comments today. So--

DR. SINGPURWALLA: I thought so, but I wanted to see what the protocol was.

DR. BOEHLERT: Okay. Thank you. That's

fair.

CHAIRMAN KIBBE: Okay?

DR. WEBBER: One quick question.

CHAIRMAN KIBBE: Go ahead.

DR. WEBBER: That will be okay?

You mentioned the pharmaceutical manufacture and research study, and I'm looking at the dates there. It seemed like it was fall of 2003. And I just wanted to confirm whether or not--that was during the period of transition of products from CBER to CDER. Were our products in OBP--the biotech products that transitioned over--were they--are they completed now within CDER? Or are they considered part of the CBER.

DR. BOEHLERT: Yes, I think Ajaz

DR. HUSSAIN: No, Keith, that's not--that's an external study that's focusing on all of manufacturing. So all products--CDER and CBER--products are under. It doesn't matter where--

DR. WEBBER: Where they were--just all products--okay. Thank you.

CHAIRMAN KIBBE: Anybody else? Good, that will keep us pretty well on schedule.

I have now a "Parametric Tolerance Interval Test for Dose-content Uniformity"--Robert O'Neill.

Parametric Tolerance Interval Test for Dose-content Uniformity

DR. O'NEILL: Magic button. There we go.

Good morning. I'm Bob O'Neill. I came before at the last meeting--I was asked to be the chair of a working group that you all blessed, and I'm here to give you an update on where we are on this issue of addressing the specifications for the delivered dose--uniformity of inhaled nasal drug products.

[Slide.]

Just to refresh your memory, the folks on the left-hand side are the FDA folks who are part of this working group, and some are more active than others--some of them, in blue, are part of a sub-group that has been put together that is working on more specific issues that I'll address

in a moment; and the folks on the right--Michael Golden, in particular, who is a colleague on the industry side, who is coordinating our efforts in that area.

[Slide.]

The objective of this working group--as you probably know--is to develop a mutually acceptable standard delivered dose uniformity specification--that's both the test and the acceptance criteria--for the orally inhaled nasal drug products, with a proposal to come back to you all. And that's the time frame that I'm talking about right now.

So there's been a lot of work going on in the past few months, and that's what I just wanted to bring you up on.

[Slide.]

There have been three full working group meetings, where the folks on that previous slide--and some others--have come together at FDA for two, three hour sessions, and to go through information that has been presented to--primarily

by the industry--to us to chew on. And we have spent a lot of time internally talking to ourselves, and coming up with some additional issues and proposals, and we met the last time with the working group, and FDA had a proposal that we felt was moving in the direction of what everybody wanted.

Subsequently, there's been a working group that will now be chewing on what was presented to the last joint meeting, and they're meeting November 4th. And there's a lot of statistical issues; there's data analysis issues. But I think what we're all on the same page with regard to is that the need to reassess the FDA--the past FDA recommendations, and I think there's--as we indicated the last time we briefed you--that the parametric tolerance interval approach is an improvement in a value-added type of testing strategy, over and above the zero tolerance interval strategy that's been used for awhile.

So the next steps are the following.

[Slide.]

This working group is meeting--the sub-group is meeting in November, and we hope that they will then come back to the full working group by the end of the year, and we will evaluated the iteration between the FDA modification to the proposals that have been made by IPAC--and this has a lot to do with the placement of the operating characteristic curve for the acceptance criteria. Essentially, there have been many operating characteristic curves that have been shown to you, some of which are more steep, some of which are more shallow. But where the proposal is being evaluated right now is: how good is it at getting from an acceptance or rejection perspective, those assays that essentially are off target mean. You can look at the performance characteristic, or an operating characteristic curve of a testing strategy if you assume that it's 100 percent on target. But the more you move away from 100 percent on target, the more you look at how well does it grab that, and how robust is it to allowing you to be a little off 100 percent?

[Slide.]

And so we're in the stages of looking at the statistical performance characteristics of that, and we hope that the working group will evaluate this proposal in more detail, and come back to you in the spring of 2005, with a final recommendation to discuss with you. So that's sort of the game plan.

And Michael Golden is here. He's my colleague on the working group from the industry side, and we'd both be willing to take any questions if you have them.

CHAIRMAN KIBBE: Questions?

Nozer?

DR. SINGPURWALLA: Well, I guess Jurgen's hand went up before mine. So--

DR. VENITZ: Okay, let me go first.

DR. SINGPURWALLA: He may ask the same question.

DR. VENITZ: Maybe.

In your draft proposal--or what you're considering so far to be a draft proposal--

DR. O'NEILL: Yes.

DR. VENITZ: --are you considering the intended use when you look at statistical characteristics of your operating curve, for example?

DR. O'NEILL: Well, certainly that has been discussed, both from an emergency--a one-time-only, a chronic use, a medical risk involved--

DR. VENITZ: Right.

DR. O'NEILL: --so, certainly, Dr. Chowdhury is involved, and others are involved, in considering this issue. So--

DR. VENITZ: And I would encourage you to do that because, obviously, in my mind, it is different whether you're looking at inhaled insulin--

DR. O'NEILL: Right.

DR. VENITZ: --and you're looking at the performance of a drug product, versus a beta agonist, for example.

DR. O'NEILL: Yes.

CHAIRMAN KIBBE: Go ahead.

DR. SINGPURWALLA: Dr. O'Neill, we had this discussion when you made the first presentation, so I'm going to back--

DR. O'NEILL: Right.

DR. SINGPURWALLA: --to the same point again.

I agree with you that tolerance interval approach is to be preferred to the zero tolerance, or something to that effect.

DR. O'NEILL: Right.

DR. SINGPURWALLA: But in your description of the next steps, you have talked about operating characteristic curves, and performance characteristic curves. Of course those are not indicative of any Bayesian thinking towards this particular area. And while you're in the process of formulating your plans, I strongly encourage you to incorporate that into your thinking. You may not want to adopt towards the end, but at least it should be evaluated.

And the second comment I'd like to make is

that--and I'm certainly not volunteering and, if asked, I would refuse--the working group members consists of individuals from the FDA and from the pharmaceutical industry. It would be good to have some neutral people on the working group--people from industry or people from government agencies that are not connected with the FDA, so that you get some sense of balance. Otherwise, it seems to be--you know, it seems to be a self-serving group.

So I would like to encourage you to expand your membership.

DR. O'NEILL: Yeah.

DR. SINGPURWALLA: And I want to emphasize: I'm not available.

DR. O'NEILL: Well--no, the last point--I mean, this is hard work. The people who are doing this work are spending a lot of time, and there's a lot of evaluation--a lot of data evaluation going on. We were presented with information from the IPAC group that consisted of a huge database.

And one could look at, well, how much time do you want to spend on evaluating a huge database?

I mean, it's an electronic database, and lots of different--and where I'm going to on this is the Bayesian argument. The Bayesian argument is very much a sensible argument--or a sensible framework when you can look at empirical data that allows you to feel pretty comfortable about what your priors are, and what the distribution of information is. That is not always accessible to the agency. It may be accessible to a sponsor.

So the strategy of being in-process and out-of-process, and being in control, and what's acceptable variability is very much--very much--a Bayesian framework, and very much within the context of how you may want to be looking at this, in terms of looking at in-process validation, as well as acceptance criteria.

The extent to which that carries over into the type of testing we have to be very clear about. And it's--at the point we're at right now, we're essentially most interesting, or most concerned about how far out can you push the acceptance curve so that it has a proper balance between accepting

and rejecting--particularly when we don't have, or no one can show us empirically, what the distribution of off-target means are, for example. How far away from 100 percent does the mean have to be before you want to maybe ratchet in this operating characteristic curve?

So, I certainly could see the value to external folks' helping us out. The more the better. And I believe that this is a time-intensive effort. And just as, you know, you would not like to volunteer, we would have to go and find folks who could invest the amount of time that is necessary, in the time frame that we're talking about, so we can get where we want to be.

That's not to say that more brains are not--and independent brains--are--but this is--I would say we're pretty much trying to meet in the middle of this whole thing with resources that we've thrown out it that we feel are fair and objective.

DR. SINGPURWALLA: Let me clarify.

I'm not volunteering because I'm making

the suggestion.

DR. O'NEILL: Yes. Yes.

DR. SINGPURWALLA: And that's the proper thing to do.

What I would like to encourage you is to involve at least two Bayesian's on your group--two, because they need support--

[Laughter.]

--from the point of view of simply guiding a framework, or guiding the concept, and things like that, rather than get involved with the nitty-gritty.

And the two individuals--or perhaps more--need not come from two stratified groups. They should come from somewhere else.

So I'm making two suggestions: one is to have people with expertise in Bayesian statistics involved, and to have people from outside these two communities also involved--perhaps in a limited way. This will give you a broader perspective and will not subject you to criticism two years down the line.

And that's the suggestion.

DR. O'NEILL: Okay.

CHAIRMAN KIBBE: Anybody else?

Ajaz, do you have something to say? Reaching for your mike?

DR. HUSSAIN: I think the point I was going to make was, I think, at this point in time it's going to be difficult to add more people to the working group. But the point is well taken that I think you do need to bring that perspective. And I'm hoping this Advisory Committee, and some other format, could be sufficient to sort of bring that framework for that--that perspective to bear on the progress of this working group.

CHAIRMAN KIBBE: No one else?

Thank you Dr. O'Neill. Appreciated your presentation.

Dr. Ajaz, perhaps you could begin our next topic, and then we can take a break, because we're running slightly ahead, and it will give us a little flexibility as we move on.

And so we're going to talk about Critical

Path Initiative.

The Critical Path Initiative--Challenges and Opportunities

Topic Introduction and OPS Perspective

DR. HUSSAIN: Yes, I think I'm pleased that we have more time, because many of the presentations here are very lengthy presentations--[laughs]--including mine.

I'd like to sort of introduce the topic of Critical Path Initiative--the challenges and opportunities.

[Slide.]

The goals that we have for the fiscal year 2005--and the initiatives, and the strategic goals at FDA level and the Department level are shown on this slide. And the slide is from the "State of CDER" address by Steve Galson and Doug Throckmorton.

Today, our discussions will primarily focus on the Critical Path, the cGMP initiative, focused on risk management and innovation. And the goal at the Department level is to increase science

enterprise research. But also, I think the follow on biologics, follow-on proteins, I think is interconnected to all of these discussions.

[Slide.]

My focus today is to introduce you to the topic of Critical Path, and also outline a proposal that we are contemplating at the OPS immediate office level as an umbrella proposal for all the discussions you'll hear today by scientists from different parts of the Office of Pharmaceutical Science.

But at the same time, some of the discussions in here also impact, say, counter-terrorism effort and other efforts that are ongoing. And not all projects that we'll discuss are Critical Path projects today.

[Slide.]

What is Critical Path? It's a serious attempt to examine and improve the techniques and methods used to evaluate the safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture.

[Slide.]

In the continuum of drug discovery and development, you really go from basic research to prototype design or discovery, to preclinical development, clinical development, to an FDA filing and approval. You have a focused attempt, say, for example, at the National Institutes of Health on translational research. The Critical Path research does overlap with some of the aspects of the NIH translational research, but it covers predominantly the drug development aspects of the entire sequence.

In our White Paper, we identified some of the challenges for Critical Path. The drug development process--the "Critical Path" is becoming a serious bottleneck to delivery of new medical products.

[Slide.]

Our research and development spending has been exponentially increasing. And as an index of 1993, you can see the exponential increase from 1993 to the current 10 years--increase in both

private and public spending on research.

[Slide.]

However, new product submissions have remained flat--or, some would argue, are on the decline.

[Slide.]

Why is FDA concerned? FDA's mission is not only to protect but also to advance public health by improving availability of safe and effective new medical products.

[Slide.]

FDA has a unique role in addressing the problem. FDA scientists are involved in reviewing during product development--they see the successes, failures and missed opportunities. FDA is not a competitor, and can serve as a crucial convening and coordinating role for consensus development between industry, academia and government. FDA sets standards that innovators must meet. New knowledge and applied science tools needed not only by the innovators must also be incorporated into the agency's review process and policy.

[Slide.]

The challenge is how do we proceed? It should be a science-driven and shared effort, drawing on available data, need to target specific, deliverable projects that will improve drug development efficiency. It cannot just be an FDA effort. We can identify problems and propose solutions. Solutions themselves require efforts of all stakeholders. We have issued a Federal Register notice requesting input from broad stakeholders, and we have received a number of suggestions, and we are working through those suggestions as we formulate our strategy for a Critical Path research program.

[Slide.]

This is a significant initiative, and the Department of Health and Human Services' Medical Technologies Innovation Taskforce is providing broad leadership. Dr. Lester Crawford is chair of this Medical Technologies Innovation Taskforce, and it includes CDC, CMS, NIH and FDA.

This taskforce is working on finding

additional funding to meet the needs of the Critical Path program. It is meeting with external stakeholders to identify opportunities, enlist allies, and so forth.

[Slide.]

In summary, I think from a Critical Path perspective, the present state of drug development is not sustainable. We believe FDA must lead efforts to question any assumptions that limit or slow new product development: are these assumptions justified? Are there more efficient alternatives? If so, why are the alternatives not being utilized?

[Slide.]

As we sort of focus on the discussions today, I'll remind you that the Office of Pharmaceutical Science is predominantly focused on one aspect: Chemistry Manufacturing Control--or the initialization dimension. But the Office of Pharmaceutical Science also supports many other aspects, from pharmacology, toxicology to clinical pharmacology research and so forth. So, although

our review responsibilities predominantly are on the quality side, our research programs are interconnected to every aspect of the drug development process.

So you will hear presentations coming from all aspects--all three dimensions of the Critical Path.

[Slide.]

The three dimensions are: assessment of safety; how to predict if a potential product will be harmful; assessing efficacy; how to determine if a potential product will have medical benefit; and, finally, industrialization--how to manufacture a product at commercial scale with consistently high quality.

[Slide.]

Our discussions, to a large degree, have focused on the third dimension. And I think you will see, today, many of the projects within OPS that also impact the other two dimensions.

[Slide.]

In our White Paper, we defined the three

dimensions and the connections to the Critical Path as follows: safety, medical utility, and industrialization. An every aspect--every box that is there has a need for improvement and research to support that improvement.

Applied science is needed to better evaluate and predict the three key dimensions on the Critical Path development.

I just returned from Europe--spending a week there last week--and with respect to the industrialization dimension, I came back somewhat depressed. The amazing work I saw coming out of the University of Cambridge in the area of industrialization of pharmaceuticals--the approach to new technology, in terms of manufacturing, novel drug delivery systems and manufacturing processes itself, was astounding. I don't see any of that in the U.S.

So my concern is, much of the R&D and innovation is going to come from Europe and Japan, probably. And unless we really improve our infrastructure, we are going to be lagging behind

in a very significant way. And I think that concern keeps growing on me, and I think I do want to sort of emphasize that.

[Slide.]

Office of Pharmaceutical Science programs and Critical Path Initiative--the discussion today is to seek input from you and advice, on aligning and prioritizing current OPS regulatory assessment and research programs, with the goals and objects of the Critical Path Initiative. Please note that not all research programs and laboratory programs are intended to focus on "Critical Path." There are equally important other aspects--bio-terrorism and so forth--which may not be considered as part of the Critical Path Initiative, but they're equally important. So all of our programs and projects are not likely--or should not be part of the Critical Path. There are aspects. So you have to distinguish that.

We hope that you'll help us identify gaps in our current program; identify opportunities for addressing the needs identified by the Critical

Path Initiative.

[Slide.]

What I'd like to do today is--before I introduce Keith Webber--he took the lead on putting this program together--I'll share with you an OPS immediate office project that Helen and I have been developing. These are our initial thoughts of how an umbrella project, within the OPS office, will help to sort of bring all of this together.

So let me share some of our thoughts on a Critical Path project that OPS--Helen and I are sort of developing right now.

An immediate need in OPS is to ensure appropriate support of general drugs--the growing volume and complexity of applications. That's the challenge. You saw the numbers increasing.

In the New Drug Chemistry, the new paradigm for review assessment and efforts to support innovation and continuous improvement goals of the cGMP initiative--Office of New Drug Chemistry has taken the lead to be the first office to sort of implement all of this. So they have

significant need for support.

Biotechnology products--complete integration into OPS, and the evolving concept of "follow-on protein products"--although I have put follow-on protein products under this, we don't know exactly how the regulatory process will evolve. It could be--let's say, a work in progress.

And, clearly, alignment of research programs in OPS to meet our goals and objectives.

[Slide.]

So what are our thought processes, from our immediate office perspective? To develop a common regulatory decision framework for addressing scientific uncertainty in the context of complexity of products and manufacturing processes in the Offices of New Drug Chemistry, Biotechnology Products, and General Drugs.

Regardless of the regulatory process, regardless of regulatory submission strategies and so forth, we believe we need a common regulatory decision framework--a scientific framework--for

addressing the challenges.

[Slide.]

What are the motivations here? Uncertainty--whether it's variability or knowledge uncertainty--and complexity are two important elements of risk-based regulatory decisions. A common scientific framework, irrespective of the regulatory path or process for these products, will provide a basis for efficient and effective policy development and regulatory assessment to ensure timely availability of these products.

That's the overreaching OPS goal, is to provide the common framework. Although the submission strategies might be different, the science should not be different.

[Slide.]

How are we trying to approach this challenge? We know that there are no good methods available for developing a standard approach for addressing uncertainty. That means you need different approaches for different assessment situations. [Laughs.] All right, let me complete my

thoughts.

So what we are thinking about--a decision framework for selecting an approach for addressing uncertainty over the life cycle of products is what is needed. So you may have different approaches and so forth, but a common decision framework will help us identify the right approach.

[Slide.]

Project 1 is to create an "As Is" regulatory decision process map for the Office of New Drug Chemistry, Office of Biotechnology Products, and Office of Generic Drugs. Much of this work will be done through a contract--we plan to have a contractor come in and work with us on some of these things.

We think a representative sample of product applications could be selected for mapping the scientific decision process in the three offices.

[Slide.]

Determine regulatory processes efficiency and effectiveness, using metrics similar to that

what we have learned from the manufacturing initiative; and identify and compare critical regulatory review decision points and criteria in the three different offices; evaluate, correlate and/or establish causal links between review process efficiency metrics and critical decisions criteria, and available information in the submission--that's the mapping process; and, also, evaluate the role of reviewer training and experience, and how it bears on some of these decisions.

[Slide.]

Summarize available information on selected products; collect and describe product and manufacturing process complexity, post-approval change history, and compliance history--including, when possible, adverse event reports that come through MedWatch and other databases; describe product and process complexity and uncertainty with respect to current scientific knowledge; information available in submissions; reviewer expert opinions and perceptions; and, if feasible

or possible, seek similar information from the sponsors or company scientists on these same products that we might select.

[Slide.]

What we hope to do is aim for the following deliverables: organize Science Rounds within our office to discuss and debate the "As Is" process map, and the knowledge gained from the study; identify "best regulatory practices" and opportunities for improvement--these may include opportunities for improvement of filling the knowledge gap, develop a research agenda for all OPS laboratories based on what we learn.

What is, I think, missing today is a common scientific vocabulary. There's a need to develop a common scientific vocabulary to describe uncertainty and complexity. There can be--each come from a very different perspective right now.

Develop an ideal scientific process map for addressing uncertainty and complexity; adapt an ideal scientific process map to meet the different regulatory processes.

In the following--I think the three projects that we're thinking about are not actually fully independent. They're all connected together.

[Slide.]

Project 2 is to sort of focus on a systems approach. We believe that without a systems approach to the entire regulatory process--that is from IND to NDA--Phase IV commitments and cGMP inspection, the broad FDA goals under the cGMP and the Critical Path Initiatives will not really be realized.

[Slide.]

So the team approach and the systems perspective that evolved under the cGMP Initiative only addressed a part of the pharmaceutical quality system. Quality by design and process understanding to a large extent is achieved in the research and development organization. Pharmaceutical product development is a complex and a creative design process that involves many factors, many unknowns, many disciplines, many decision-makers, and has multiple iterations in the

long life-cycle time.

So we have to treat it as a complex system optimization problem.

[Slide.]

Significant uncertainty is created when a particular disciplinary design team must try to connect their subsystem to another disciplinary subsystem--for example, clinical versus chemistry, or CMC to GMP. When you bring those connections, there's significant uncertainty.

Each subsystem can have its own goals and constraints that must be satisfied along with the system-level goals and constraints. It is possible that goals of one subsystem may not necessarily be satisfactory from the view of other subsystem and design variables in one subsystem may be controlled by another disciplinary subsystem. Impurities is a good example. Pharmtox, CMC, and how you bring that together.

[Slide.]

So the Project 2 proposal that we're developing is to use ICH Q8 as the bridge between

the cGMP Initiative and the rest of the regulatory system, and to develop a knowledge management system to ensure appropriate connectivity and synergy between all regulatory disciplines. Can that be done? I mean, that's the feasibility project that we are trying to develop. So--connect Pharm/Tox, Clinical, Clinical Pharmacology, Biopharmaceutics, CMC, Compliance all together.

[Slide.]

The current thinking is to approach this problem as connecting every section within the ICH Q8 CTD-Q, within the same document, but to all other sections in an NDA, in some way or form. For example, each section within the P2 can have an impact on the other P2 sections and, similarly, other sections of a submission and to cGMP.

By recognizing this as a complex design system that involves multiple attributes, goals, constraints, multidisciplinary design teams, different levels of uncertainty, risk tolerances, etcetera, we wish to find opportunities to identify robust designs and design space that provides a

sound basis for risk assessment and mitigation.

So this would be a scientific framework. It was a regulatory tool that could come out of this. And with the case studies and everything coming together, this might be a way to bring and connect all the dots.

[Slide.]

What we have been looking out is outside pharmaceuticals. We believe that a significant body of knowledge exists. Example, in mechanical engineering, as it applies to the design of aircrafts, that addresses some of these challenging points that we have discussed. These are three examples that I have selected as just illustrative examples of how multidisciplinary optimization methods and system-level problem solving tools can be thought about in the drug context.

[Slide.]

Just to illustrate this point, let me create an example here. The applicability of multidisciplinary optimization methods for solving system-level problems and decision trade-offs will

be explored in an NDA review process. That's what we're proposing.

For example, in the Common Technical Document for Quality--the P2 section, which is what ICH Q8 will define--critical drug substance variables that need to be considered in section 2.2.1, which is "Formulation Development" are described in section 2.1.1. So there's a drug substance, and there's a formulation. They're two different sections.

Information for "Drug Substance," has a bearing on that of the "Formulation Development." So how do you connect the two together?

For example, the current language in ICH Q8 for "Drug Substance," states: "Key physicochemical and biological characteristics of the drug substance that can influence the performance of the drug product and its manufacturability should be identified and discussed."

So that's describing the information content in section 2.1.1. that we will hopefully

receive whene ICH Q8 is done. So how does this have a bearing on the "Formulation Development" section?

[Slide.]

I'll skip this and just show you a figure.

[Slide.]

You have the API--or drug substance manufacturing process. The X(1.1) is the design variable; the f(1.1) is the objective function to be addressed; and the g(1.1) is the constraint for that manufacturing process that delivers the drug substance. Okay?

Since this is not part of ICH Q8, what will be part of ICH Q8 is section 2.1.1., which will identify what are the critical variables for the drug substance, as they relate to the formulation aspect. But that becomes the input for what--how it connects to the "Formulation Development" aspect. And that link is through a linking variable.

Since my means and standard deviations have become finger-pointing and so

forth--[laughs]--so you know--you have a design variable, you have a linking variable, you have an objective function, you have constraints around which you define your design space. You have mean objective function--that's your target. You have a standard deveiation that you sort of bring to bear on that. And deviation range of the design solution, or the design space.

So all of this sort of has to come together for this to be meaningfully connected. And, for example, if you start with a simple design of experiment, you may have mathematical models, which are empirical, but then they provide that connectivity. So it's a start of a very formal, rigorous approach to dealing with uncertainty, knowledge gaps and complexity.

So this might be a useful concept. So that's the process right now, to see whether this could be a feasibility project that we could do.

[Slide.]

So the potential deliverables of using this approach could be significant. Since we are

moving towards electronic submissions, in conjunction with electronic submissions, this project can potentially provide a means to link multidisciplinary information to imporve regulatory decision--that is, clinical relevance to CMC specifications. We may not all have all that information, but the links--the structure--will be there as we grow, as we improve our knowledge base, or will it be refined, the links could get populated, and this might be an approach for knowledge management within the agency.

Creating a means for electronic review template and collaboration with many different disciplines; provide a ocmmon vocabulary for interdisciplinary collaboration; create an objective institutional memory and knowledge base; a tool for new reviewer training; a tool for FDA's quality system--and, clearly, it can help us connect cGMP Initiative to the Critical Path Initiative.

So that's the project that we hope to develop. We really want to get some feedback from

you, and develop this as a project under the Critical Path Initiative.

[Slide.]

But the third aspect of this--it all could happen in parallel--explore the feasibility of a quantitative Bayesian approach for addressing uncertainty over the life cycle of a product. The most common tool for quantifying uncertainty is probability. The frequentists--the classical statisticians--define probability as "limiting frequency, which applies only if one can identify a sample of independent, identically distributed observation of the phenomenon of interest."

The Bayesian approach looks upon the concept of probability as a degree of belief, and includes statistical data, physical models and expert opinions, and it also provides a method for updating probabilities when new data are introduced.

The Bayesian approach may proivde a more comprehensive approach for regulatory decision process in dealing with CMC uncertainty over the

life cycle of a product. It may also provide a means to accommodate expert opinions.

And I think there's a connection here. The evolving CMC review process may be a means to incorporate expert opinions. And I think that is a significant opportunity.

Using the information collected in Project 1--that I described--you would seek to develop a quantitative Bayesian approach for risk-based regulatory CMC decision in OPS.

So that would be a project that will run in parallel to the other two approaches that we are moving forward.

[Slide.]

So, I'll stop my presentation here with sort of summarizing, in the sense--I think OPS, from its goals and objectives, has to have an overreaching project that sort of connects all the dots together. And the proposal--the first one clearly is a process map--"As Is" and so forth. But the two others are feasibility projects that we want to look at the Bayesian approach and a complex

system optimization problem.

The knowledge exists outside. It's simply adapting and adopting it in our context.

What you'll hear--after the break, I think. Or--unless you want to start earlier--after the break, is other immediate office projects; Office of Biotechnology projects, Office of New Drug Chemistry project, Office of Generic Drug projects on Critical Path, and Office of Testing and Research.

What we have done is Keith Webber will introduce the reset of the talks. You will hear each group's perspective. And we have requested Jerry Collins to come back and sort of summarize--after his talk on the Critical Path--the entire Critical Path Initiative from an OPS perspective and pose questions to you.

And we have also invited Professor Vince Lee, who is now part of FDA--who used to be the chair of this committee--who has been with agency for almost a year now, to come with his perspective on how--what are challenges he sees. So you will

hear sort of presentations and some opinions from people who have been at the agency and been looking at this challenge for some time.

So, again, the discussion today is to seek input and advice on ACPS; on how to align, identify gaps, and identify opportunities.

I'll stop here and entertain questions on my part of the presentation.

CHAIRMAN KIBBE: Are there any questions?

DR. SINGPURWALLA: I have comments.

CHAIRMAN KIBBE: Okay. Thank you.

DR. SINGPURWALLA: I just--what you say is music to my ears. You have good vision about some of the things you want to do. But I think it's now time that the dance should begin.

We should get back--take concrete problems and address them. I've said this before.

But let me just make some specific comments on some of the things you've said. And, of course, I'm going to question some of the things you said.

The first argumetn I want to make on your

slide on page 7, about efficacy and safety: generally, those tend to be adversarial. Drugs that give you benefit may have side effects. So the important issue is to do a trade-off. For that you need to talk about assessing utilities: what is the utility of the benefit, and what is the dis-utility of the harm? That's a part of the whole package of thinking about these problems, and I encourage you to look into it.

Now, I take strong objection to some of the things you have said. You have distinguished uncertainty into stochastic and epistemic. I have seen that distinction before. I claim it's totally unnecessary. Uncertainty is uncertainty, and one doesn't--one should not pay much attention to the source of the uncertainty--

DR. HUSSAIN: Right.

DR. SINGPURWALLA: --whether it is regulated allatoire uncertainty, or epistemic, does not matter.

CHAIRMAN KIBBE: Right.

DR. SINGPURWALLA: The Bayesian approach

does not distinguish between the two. And since you've been talking about it, I think--

You also say that there are no good methods for devleoping standard approach for addresing uncertainty. I think that's the wrong slide to put up. That's liable to do more harm than good.

DR. HUSSAIN: Okay.

DR. SINGPURWALLA: There are methods available. So I would not encourage you to put it.

And the other thing is: I don't like your linking uncertainty and complexity. They're two different issues.

And you also say that there is no common scientific vocabulary. Well, I claim there is a common scientific vocabulary, and that is probability.

Now, as far as recommendations are concerned: I'd like to suggest--and, again, I'm not volunteering since I'm making the suggestion--that you have your people exposed to a tutorial on Bayesian methods and Bayesian ideas, so

that you get a better appreciation of what it's all about. And the best way to do this is to take a simple example and work through it; work through your expert opinion notions that you're saying.

Go through an example, and you'll get a better appreciation of what it's all about. And once you get that appreciation, you'll be tempted to remove some of the other things you've said.

Those are just comments. Thank you.

DR. HUSSAIN: No--the point's well taken. And we actually have a project right now with the University of Iowa, looking at our stability data from a Bayesian perspective. So we're just starting to put a real-life example on that. So that's--

With regard to the utility, Jurgen and the Clinical Pharmacology Subcommittee has been sort of bringing that up. So we will connect to the Clinical Pharmacology group.

Jurgen, do you want to say anything about that?

DR. VENITZ: [Off mike.] Well, other than

the fact that--other than the fact that we're discussing it. It is a controversial issue, because you're really trying to map, then, a lot of different things into a uniform scale. Personally, I don't see an alternative, and I think it's already done. We're just doing it intuitively, as opposed to expressedly.

So it is being discussed. We have to see where it goes.

DR. HUSSAIN: And, regarding, I think, the common vocabulary, I think it's a common vocabulary in the context of when we speak from a pharmacist to a chemist to an engineer--we have very different interpretation--that's what was referred to.

DR. SINGPURWALLA: That's why you need a tutorial.

DR. HUSSAIN: That's exactly--

DR. SINGPURWALLA: Put people together. Because about 15, 20 years ago, the Nuclear Regulatory Commission was facing similar problems. And one of the things they did is they had lots of tutorials to get everyone on board, talking the

same language. Otherwise, you'll have a doctor talk to an engineer, and those two talking to a lawyer--and you know what can happen.

[Laughter.]

VOICE: [Off mike.] Lawsuits.

CHAIRMAN KIBBE: Another question?

DR. KOCH: I guess, just to build on the last comment--when you get into all those multidisciplinary functions--and particular when the ICH Q8 is going to serve as a group, together with the implementing the cGMPs--there's a couple of organizations out there I think could serve as very valuable resources. One we've heard about a couple times today in the ASTM 55, as a body to help at least standardize the terminology. And the other one is the ISPE, which could serve as a multidisciplinary conduit that, working together with ICH, could probably facilitate some of the multidisciplinary issues.

DR. HUSSAIN: I think we do plan on extensive training and team building and coming on the same page. If you look at the PAT and the

manufacturing signs White Paper that we issued, we actually laid out a lot of these things in there, including the role of ISPE, ASTM, PQRI, and so forth.

So we have been thinking about this in that context, and at the ICS meeting in Yokahama--on Wednesday, I think, the date is set--we will be updating on that. So I'll get a chance to talk about ASTM to ICH in Yokahama, Japan, also.

So, we're aligning everything together. So that's happening.

There was one point that I wanted to respond to: the reason for keeping uncertainty, in terms of variability in knowledge--keeping the distinction, at least as we think about this, was--and the link to complexity, also--clearly, complexity and uncertainty are two independent things. But, unfortunately--well, the challenge we face is this--in the sense we have a very complex product. We have simple products--within the same office, in OPS and different regions. Yet today, I

think, from a variability perspective, we're not very sophisticated in how do we deal with variability.

And, for example, in our manufacturing science White Paper, we don't even deal with variability of our dissolution test method. We don't even know how to handle it. So we have challenges today where simple variability--we don't have a good handle on.

So that was the reason for keeping variability and knowledge-based uncertainty on the table.

CHAIRMAN KIBBE: Ken?

DR. MORRIS: Just a quick question: on your identification of the gaps in the current programs, are you thinking more in terms of technical gaps--as in science that needs to be done? As opposed to logistical gaps within--

DR. HUSSAIN: Both. Both.

DR. MORRIS: So, with respect to the scientific gaps, are thinking, then, to take it one level more--basically, are you talking more about

new science that needs to be created? Or science that needs to be communicated more effectively--within the agency?

DR. HUSSAIN: Well, I think the immediate need would be to communicate the existing science and bring all the existing knowledge to bear on that. And, clearly, in the long term there are fundamental issues--and most of the new science would be needed. So I think it's an issue of timing.

DR. MORRIS: Thank you.

CHAIRMAN KIBBE: Anybody else? Nozer, you wanted to--

DR. SINGPURWALLA: No, I just wanted to say that this distinction between allatoire and epistemic has been artifically created by frequentist statisticians. And Bayesians don't buy it.

DR. SELASSIE: I have a question.

CHAIRMAN KIBBE: Yes, please.

DR. SELASSIE: You know, in your graph on R&D spending--has there ever been a breakdown in

how much of that spending can be attributed to the "R" and how much to the "D?"

DR. HUSSAIN: I don't have that--I'm sure that information's--I don't have it. So I'm not aware of it.

DR. SELASSIE: Because would one parallel, you know, the flatness?

DR. HUSSAIN: One was the public funding; one was more private funding, so--

DR. SELASSIE: Yes, but they're both going up.

DR. HUSSAIN: Yes.

DR. SELASSIE: But I'm wonder if, you know--because you look at your product submissions are flat. Now, is that because there's not been an increase in development funding? Or--

DR. HUSSAIN: I don't think so. But I don't have an answer.

DR. SELASSIE: Yes.

DR. HUSSAIN: So let me say that.

CHAIRMAN KIBBE: Marvin?

DR. MEYER: Ajaz, you don't seem like a

depressive kind of guy--

DR. HUSSAIN: [Laughs.]

DR. MEYER: --but you said you were depressed last week.

DR. HUSSAIN: Yes.

DR. MEYER: Can you give us just a real short synopsis of where you see Europe doing things right, and us doing things wrong?

DR. HUSSAIN: [Sighs.] [Laughs.]

No, I mean, again, I'll focus on what I see happening in Europe--especially in the U.K.--and how they're translating academic research--academic finding research--into entrepreneurial business--in particular in manufacturing, in particular in dosage form design--the pharmacy-related ones.

Look at Bradford, particle engineering. And the one I saw--I saw a beautiful manufacturing system for coating. Forget coating pans. This is electrostatic coating; precise, automated, complete on line, and so forth.

Nothing of that sort is happening

here--within my domain.

CHAIRMAN KIBBE: We have a couple more comments, and then we're going to have to take a break.

Go ahead.

DR. MORRIS: Yes, just to follow up on that. I think there's--I just came back from Europe depressed, as well, but I was in Scandinavia. So maybe that had something to do with it.

[Laughter.]

Yeah, it's pretty dark up there.

But, in any case, I agree with Ajaz in that there are a couple of caveats and, in fact, if you look at our latest hires, they're one from--via Bradford, another one via Bath. My post-doc is from Nijmwegin, another post-doc from Roger Davies Group in the U.K.

And we're not training people--number one. So, aside from not transferring the technology effectively we're not training people to do it very much any more. There are few places--represented

at the table--that still do it to some degree.

But that stems back to one of your earlier slides, which is trying to muster NIH and NSF to fund this sort of research. Because some of you have been a lot closer to deanships than I. If there's no overhead money, it doesn't get a very kind reception. And the fact of the matter is is we haven't had it.

So, this is--I'll stop here, because this is my old soapbox. But I lay this at the door, in part, of NIH and NSF for not recognizing, in the face of overwhelming data, that there is a crisis that needs to be address.

On the upside, there are some people in Europe doing some things--and Japan, as well.

CHAIRMAN KIBBE: Pat, go ahead.

DR. DeLUCA: Just a quick follow up on that, too. I know from my trips to Europe, too, if you just look at the colleges--the pharmacy schools in Europe--I mean, they all have departments of pharmaceutical technology. I mean you'll be hard-pressed to find pharmaceutical technology as

an area of focus in an American college of pharmacy now. Certainly you won't see any departments of pharmaceutical technology.

So I think it's been--and it wasn't that way 20 years ago. But, I mean, it certainly has changed, though.

CHAIRMAN KIBBE: Anybody else?

Good--I think we're at a nice break point. And if we could take perhaps a 10 minute break--because Ajaz has managed to get us--use up all of our lead time.

[Laughter.]

And we can get Keith to start his talk at about 10:22, that would be great.

[Off the record.]

CHAIRMAN KIBBE: 22 minutes after 10 has arrived, and one way or another we're going to get back on process.

Dr. Webber, are you prepared to get on process?

He's on the way to the podium.

Those of you walking around with cakes in

your hands, and sodas, you want to sit down.
Nozer. Here we go. Good luck. We gave you 10 minutes to do that.

[Pause.]

You snooze, you lose, as the old saying goes.

So, Dr. Webber, shall we start our Strategic Critical Path?

Research Opportunities and Strategic Direction

DR. WEBBER: Okay. I guess we're about ready to get started on this session, regarding research activities and our strategic goals for the Office of Pharmaceutical Science.
I'm Keith Webber, with the Office of Biotechnology Products. And let me--

[Slide.]

--there we go.

Ajaz went through a very good presentation, I think, on the Critical Path. And I'm not going to really address very much about the Critical Path Initiative itself. But, in my view, this--I've sort of summarized things into the Drug

Development Path, which begins with discovery of potential targets--or potential new drugs; and then you have to have a period where one evaluates the candidates and makes a selection of what candidate you should carry forward into the pre-clinical study, where one looks for potential toxicities and potential efficacies in an indication of interest.

If all goes wlel, one moves into clincal studies, and if all goes even better, into commercialization. And then, once you're on the market, there's always the period of post-approval manufacturing optimization--or we would like to see that, from the FDA's perspective, anyway.

And then, often, we get new indications--we see new indications being developed for drugs that are on the market. And that essentially starts the process back up again--often at the clinical studies stage.

[Slide.]

The--I didn't bring a pointer. Is there a pointer here?

VOICE: [Off mike.] Just use the mouse.

DR. WEBBER: Just use the mouse. Okay. That will work. Right there is the mouse. Okay.

I guess, historically, FDA interactions; have occurred primarily ion this area here, from clinical studies on. Prior to that, we have had very little influence, I think, until we receive a submission which contains information regarding the pre-clinical studies.

But I believe we have opportunities to have an impact on this entire process in the future.

Let's see.

Essentially, I guess, sort of the essence of the Critical Path is the--in my mind--is the view from empirical versus guided drug development. And drug development has to be a learning process in order to make intelligent decisions regarding such issues such as your candidate selection; what dosage form you're going to have and what the formulation should be; in choosing clinical indications, you need to know what patient population is going to be the best selection for

your product. And then when you're evaluating clinical endpoints, one needs to know which are the most appropriate endpoints to evaluate in the clinical studies, and are there surrogate endpoints that are more appropriate than others, if you can't look at an endpoint which is directly related to survival or efficacy in the more normal manner.

And, of course, with adverse event monitoring, any clinical trial is going to monitor particular parameters, and you need to have a good knowledge base in order to understand which adverse events we should be looking for, and the best way to evaluate those.

And then, finally, the manufacturing method certainly is a major concern because that has to do with the ability to improve the manufacturing process post-approval and pre-approval, as well as avoiding issues that can come up with regard to safety and efficacy of your product.

[Slide.]

The goal of industry, as well as the

agency, I believe, is to establish a knowlege base and the tools that are necessary to predict the probable success of any given product, and the manufacturing methods that are appropriate to it, and then to foster the development of products that are going to have a high likelihood of success, throughout clinical development and on the market.

[Slide.]

Now, for this late morning's presentations and this afternoon's presentations, we'll be hearing from a number of groups within OPS. One is the Informatics and Computational Safety Analysis staff, which is in--essentially in the immediate office of the OPS; and then Office of New Drug Chemistry, Office of Generic Drugs. And the first three here are the groups that do a lot of relational and database analyses as part of their research activities. There are, in some cases, collaborative research going on with laboratories, per se. But it's the groups on this--the last two, the Office of Testing and Research, and Office of Biotechnology Products, that have actual

laboratories where research at the bench is going on.

[Slide.]

Let's see--within OPS's Critical Path Research, I think we can address--or can address the issues regarding candidate selection, based upon an understanding of the structure and activity of the relationships that we see, and the products that ocme down the line, as well as what's reported in the literature.

Dosage form development and evlauation I think is an important area that we're working in. Toxicity predictions for products is--we're amenable to that, so our research can address that through, again, structure activity-type relationships and structure-function issues, as well as knowledge of the impacts that a particular disease state might have on physiological function that may lead to toxicities that wouldn't be present in all populations.

Bioavailability and bioequivalence predictions are certainly important for all of our

products, but particularly for the Office of General Drugs, they're quite critical. And I think with regard to the follow-on products as well, it's a major area of concern.

Metabolism prediction is something that is, I think, crucial because products, once they enter the body, as you know, they don't remain in their initial state. And the metabolism can impact toxicity, it can impact efficacy, it can impact the bioavailability and biofluence of the products themselves.

Immunogenicity is another area that is of large concern, particularly for protein products. And there we need to evaluate and understand, not only the caues of immunogenicity, or the impacts of various structures in the proteins on immunogenicity, but also the impact that the patient population has on immunogenicity; what impact the indication that's selected can have on impacts of immunogenicity as a safety concern.

Often, as I mentioned earlier, you have biomarkers that you're looking at for

pharmacodynamic parameters, or for surrogate endpoints. And a good knowledge of the validity of a particular biomarker, and our ability to evaluate those, as well as industry's ability to select those, is dependent upon the knowledge that they have of the biology of the disease that they're studying, or that they're trying to cure or that they're trying to treat.

The mechanism of action of the drug is certainly critical when you're looking at the potential. One area is with regard to drug-drug interactions. Oftentimes we've been looking primarily at metabolism for drug reactions, but certainly there's a concern that I think is building for utilization of multiple drugs that impact on the same metabolic--not metabolic pathways, but the signaling pathways, let's say, at the cell surface, which are getting the treatments--you know, getting a treatment into the cell, or that are resulting in the clinical effect--is what I'm trying to say, in a very poor way.

Let's see--the pharmacogenomics is a new area that we're getting involved in, but it's very important with regard to patient selection, as well as the potential for certain populations to be impacted by drugs in a unique way, that can impact not just efficacy, but also the safety.

And manufacturing methodologies are an area that we have research programs in within the office, and those are important for developing and understanding of the robustness of various manufacturing processes, and the ability to implement new paradigms, such as process technologies in the manufacturing process of pharmaceuticals

[Slide.]

Out strategy here is to coordinate cooperative research activities. And, as I mentioned, we have predictive modeling programs. And these are generally based upon information from regulatory submissions that we receive, as well as from laboratory research that's going on within the agency, as well as outside and in the published

literature.

One area which, I think, we need to build is our abilities to get information from industry that we don't get in a our regulatory submissions, and that they don't publish, and finding a means to have them help us to gain knowledge of that information so that we can implement it into the decisions we make and share that--basically the conclusions that come out of that with industry as a whole, to address the Critical Path.

[Slide.]

There's also laboratory research going on--you'll hear from the Offices of Testing and Research, Applied Pharmacology Researhc, and Product Quality Research, and Pharmaceutical Analysis--and also from my office, Biotech Products, from our divisions of Monoclonal Antibodies and Therapeutic Products--it should be Therapeutic Proteins. Sorry. Typo there.

There's also research going on in other FDA centers that we can collaborate with, and do collaborate with, as well as outside, to gain

information from academia, industry and other egoernment agencies, as well.

[Slide.]

Now, I think we can gather all this information, but it's critical with regard to how we're going to use it, and how we're going to disseminate it, such that we can have an impact on the Critical Path.

There are a number of avenues to get to academia and manufacturers, and those include the public forums, where we can present the conclusions and recommendations. We certainly write guidance documetns that can help in this manner, as well. And then, when industry comes to meet with us at the regulatory meetings, such as pre-IND, and pre-NDA meetings--pre-BLA meetings--we can interact with them at those points, as well.

But we also need to change, to some extent, our review processes within the agency, and--so the information has to go to the reviewers, as well. And we can do that via training programs, as well as the guidance documents that we do write.

They're used a great deal by the reviewers.

Then, again, mentoring programs, to bring up the new reviewers in an understanding of the new paradigms and new concerns, or lessen their concerns for particular issues that relate to pharmaceutical manufacturing, or clinical issues.

And then all of this together should help to enhance the application of your process from the reviewer's standpoint, and with regard to the manufacturers should help to remove some of the hurdles and obstacles we see in the Critical Path.

[Slide.]

You'll hear the coming presentations. So there are some questions we'd like you to keep in mind, that we'll be bringing up later for discussion.

And first is: are we focusing, within the office, on the appropriate Critical Path topics? And are there other topics that we should be addressing through our research programs? And it's both the database relational type information or research programs as well as the laboratory

programs.

And then, in the future, Critical Path issues may change. So how should we identify Critical Path issues in the future. And we'd like recommendations on how we should prioritize those. Because we're really--at this point, we can't do everything that needs to be done with the current resources, and so we're going to have to prioritize now, and in the future we'll need to prioritize, as well, and we'll need some guidance on that.

That ends my presentation. We'll move into the first talk--to stay on time--which is going to be--let's see, I'll bring it up here--Joe Contrera.

Informatics and Computational Safety Analysis Staff (ICSAS)

DR. CONTRERA: Okay. I'm the director of the Informatics and Computational Safety Analysis group. Our main mission, really, is to make better use of what we already know; material or safety information, toxicology information that's buried in our archives; and also in the scientific

literature and in industry files.

Our group develops databases and also predictive models. You can't develop models without the databases. So they go together.

We have develop our own paradigms for transforming data, because traditional toxicology data is textual, and converting into a weighted numerical kind of a scale that is amenable to be processed by computers, and also to be modeled.

And we encourage, promote and also work with outside entities to develop QSAR--qualitative structure activity relationship software--and data mining software, for use in safety analysis.

We don't work alone. And you'll hear more about this in my talk. We leverage, very much, and cooperate, and collaborate very much with outside--with academia, with software companies and with other agencies. And we do this through mechanisms such as the CRADA--the Cooperative Research and Development Agrement--which is really a buisness agreement--and also we do it with Material Transfer Agreements, for an exchange, quid

pro quo exchange, with software and other scientific entities outside the center.

[Slide.]

The Critical Path Initiative--you've all been, and you're going to be hearing more about it, and you've heard a lot about it. I'm focusing on what is relevant to my group, and that is: the problem is that we have not created sufficient tools to better assess safety and efficacy. We're still relying on toxicology study designs that were designed 50 or sometimes 100 years ago. And it doesn't mean that they're inferior, but maybe there are better ways of doing this now.

So we need a process to develop better regulatory tools. And it was really a controversy, to some extent: whose misison is this? And in the past, the agency didn't consider it as the agency mission to develop these tools--necesarily. It was academia. And academia said, "No, it's the industry." It wasn't--it was vague as to who was actually responsible for developing new analytic tools that can be used for regulatory

enpoints--especially in safety endpoints.

[Slide.]

So now how d we connect with the citical path? I think we were doing Critical Path research well before there was a Critical Path Initiative. I mean, we've been in operation, in one form another, for over a decade in the Center, at a time when people were questioning whether this was the mission of the agency in the beginning.

We developed databases and then predictive tools that are used by the industry--by the pharmaceutical industry--more and more to improve the lead candidate selection. And the question was: why should the agency supply industry with better tools to select lead candidates? Well, it's in our interest that they develop lead candidates that have fewer toxicology or safety problems. Because when they come to us, in the review process and submissions, they can said right through with very few issues. Otherwise, they'd bog down the system. And we have multiple review cycles, and there are issues to be addressed. And it would be

wonderful if they could just slide through.

And so also to facilitate the reiew process internally, by having reviewers having a rapid access to information that is usable for "decision support," we call information; that they can use to make judgments on a day-to-day basis. And we hope that also this could reduce testing; reduce the use of animals. And also encourage industry--software companies--to get into the business of developing predictive modeling tools.

[Slide.]

And we see this three-dimensional diagram for the Critical Path. Well, the computational predictive approaches are identified in two of the three pathways. And so we feel we're right in step with what the future goals of the agency are.

[Slide.]

What have we accomplished already? Well, again, we do two things: databases and predictive modeling. And this sort of summarizes some of the accomplishments; the first being we've developed predictive software for predicting rodent

carcinogenicity, for example, based on the compound structure. It's being used by the pharmaceutical companies. It's distributed by small software vendors.

We are also--obviously, we cannot screen industry's compounds in the agency. That would be a conflict of interest. But our software is being used. We have an Interagency Agreement with NIH--NIH has a drug development program--we have a contract with NIH. NIH sends us compounds that they're screening in their drug development program for treating addiction. And so we are, in our own way, practicing what we preach, in terms of using our software in lead selection in drug development.

We also--software is being used--and we lay a consulting role, within the Center, for evaluating contaminants and degradants in new drug products and general drugs, to determine--to qualify them, and determine limits. So we feel that our software could have much more application in that realm.

And decision support for review divisions.

We collaborate very closely with the Center for Food Safety. And, in fact, we're training their scientists, and have shared our software with them, and they're using our carcinogenicity predictive software to screen food contact substances. Because they're working under the new FDAMA rules that place the burden on the agency; in other words, the agency has to, within 120 days, decide whether there is a risk. The agency has to give cause why a substance is a risk. It's a reverse of sort of what drugs are.

So in order to meet those kinds of deadlines, they had to go to predictive modeling to ascertain whether there's a potential risk of a food contact substance--within 120 days.

EPA is looking at our--and we work with them. And the software also can be used in deciding whether we have a data set that is adequate; whether there are research gaps that need to be filled.

[Slide.]

So we talk about the FDA information. We

get submissions, we review them. There's an approval process, and then the post-approval process. We extract information from this process. We extract proprietary toxicology data, non-proprietary toxicology and clinical data. And we build proprietary and non-proprietary databases, so we can keep information that can be shared with the public through Freedom of Information and information that will not be shared--or cannot be shared legally--into two different databases.

And we use these databases for a variety of functions: for guidance development, for modeling. And also for decision support fo the review; and also it feeds back on industry, because much of this information can be shared with the public, because it's under the Freedom of Information Act.

[Slide.]

We have leveraging initiatives in both realms. We leverage to get support from outside to help us develop databases, so that we don't rely entirely just on FDA funding.

And the objectives are to creat specific databases--endpoint specific. They could be mouse studies, three month, 90-day studies, one year studies; the toxicology databases that people are interested in.

These database initiatives are funded and supported through CRADAs and other mechanisms. We have a CRADA with MDL Information Systems, which is a part of Reed Elsevier publishing company. They are interesting in building a large information system, and so they're helping, supporting, our effort. We have CRADAs in the works with Leadscope that has a wonderful platform for searching toxicology data. And also we have a CRADA in process with LHASA Limited, in England--University of Leeds in England--that has a system also--an interest in these kinds of databases.

What we--our databases are constructed--the center of our database is the chemical structure. It is a chemical-structure based database. And the structure is in digital form so that it can be teased--it's a

chemoinformatic database. And the digital form is called the .mol-file structure, and it's a common structure used in industry for over a decade. So the chemical structure, as well as the name is the center search point.

And then once you have a structure that's in digital form, you can not only ask a simple question about, "Can I find substance x," but you can also query and ask whether--"I'd like to know everything--all the compounds that are like it." And that's such a powerful tool--regulatory tool--that I think is another--puts us in another dimension.

It's not that I want--"Tell me about acetaminophen," but I want to know compounds that are 90 percent like acetaminophen in a data set. And we're able to do that now--really easily--with the system.

So once we have this system, then we tie in--the databases are linked to this search engine. We have our clinical databases that we model--post-marketing adverse event reporting

system, and also the tox databases. And we use all this--what we're really interested in is modeling; computational predictive toxicology.

And the sources of that data on these databases come from reviews. We extract information from the regulatory reviews and from other databases.

[Slide.]

So, now, getting into our modeling operation, we transform the data. We supply the chemical structure data, and our collaborators and software companies supply the software. And we work with them on an iterative basis to improve and make these things work, and develop software for these endpoints.

We've also, I think, are probably the first group that have developed a way of using chemical structure to predict dose. And so we have a paradigm for predicting what the maximum daily dose of a compound might be in humans, within a statistical, obviously, error bar, in humans.

So, currently, in our prediction

department, you might say, we have access to five or six different platforms. And they represent very different algorithms. And this is the point we want to have interactions with software companies that have approaches that are different from one another. And then we evaluate and work with them to try to develop models, using our data sets.

So we have two CRADAs on board right now, with multi-case and MD/QSAR, and we have others in the works. And we also have interactions with other prediction approaches from the statistical.

[Slide.]

In terms of the models that we're working on now, the objective is to model every single test that's required for drug approval. And so we started with carcinogenicity, because that was the most--the highest profile, in terms of preclinical requirement; and teratology would be next. These are endpoints that cannot be simulated in clinical trials; mutagenicity, gene tox--all these are models, either have been created or are in the

process of being created and being worked on.

We're also attempting to model human data--the adverse event reporting system; post-marketing human data. This is an enormously difficult data set; very dirty data set, but it's enormous, in terms of its size.

[Slide.]

And we have had some success, preliminary modeling, of hepatic effects, cardiac effects, renal and bladder, and immunological effects in humans. These are still works in progress, but we have made progress.

And in terms of the dose related endpoints, we have made really good progress. We were surprised, ourselves, because we didn't really think this would work. We've been able to successfully model the human Maximum Recommended Daily Dose--you know, that's the dose on the bottle when you get your drug. It says "Don't take more than 10 milligrams a day for an adult. Well, we modeled that, because that comes from clinical trial data. That is really human data. And it

represents an enormous scale--I don't want to get into it--but it's like an eight-block scale of doses, and we have 1,300 pharmaceuticals that are either--that we've modeled, in our database. And we were able to successfully model this--and I'll get back to that in a moment.

[Slide.]

The other question that came up was proprietary data and sharing industry data. It would be nice to get their data, especially in areas that we know the industry has a great deal of experience in, like gene tox data. Right now we can't have access to data that was not in submissions. And so we need a way of doing this. Chemoinformatics gives you a way of at least getting there partially. We're able to share the results by not disclosing the structure and name of a compound. You can disclose the results, but you say "What good is disclosing results, or using the results, without knowing where they came from?" Well, you can use descriptors--chemical descriptors--that can be used in modeling, but

cannot be used to unambiguously reconstruct the molecular structure. But they contain enough information to model.

And so you're sort of at least halfway there. You can share some information that can be used in modeling. And so this is a feasible approach and, in fact, it's already being accomplished--legally. It's gone through our legal--our staff at the agency and it's incorporated in some of these softwares.

[Slide.]

And this is an example. This is 74 MDL QSAR descriptors for the compound methylthiouracil. Now, these descriptors are used in modeling, and ocntain a great deal of scientific information, in terms of modeling. But all of these descriptors will not unambiguously recreate the structure of methylthiouracil, because there's a lot missing. It's like a pixel pictures. You know, you have a photograph--a digital photograph--if you've only got 70 pixels, you'll get a rough picture of what it is, but you won't know it's your uncle. It's

just a person--you know. But if you had 10,000 pixels, you'd know exactly who it is. It's the same idea. So you can share this crude image.

[Slide.]

Getting back to modeling the human maximum daily dose--at present, we have to go through many steps to arrive at a starting, Phase I clinical starting dose, in a drug that's never been into man for the first time. We start with animal studies--multiple dose studies in multiple species. So already that's a lot of cost. Then you estimate the no-effect level--has to be estimated from this. Then you have to decide which species is closed to man by looking at the ADME and, you know, metabolism and everything. And then you have to convert that to a human equivalent dose using allometric scaling. And then, on top of that, you use a little--the uncertainty factors, dealing for inter-species extrapolations--finally come up with a dose that you might try for your first dose in human--in clinical trials.

Well, if you could model, on the basis of

structure, the maximum recommended daily dose, you get a predicted dose in humans--because that's human data. You take one-tenth, or one-hundredth of that, just to be on the safe side, and you have a dose.

And what's the benefit? There's no testing in animals. There's no lab studies. There's no inter-species extrapolation, because you're using human data. And we think it's more accurate, because animal studies don't predict whether a drug is going to cause nausea, dizziness, cognitive dysfunction. Animals can't tell you that. But yet that appears in labeling for old drugs all the time.

So we feel that this is a good approach. Everyone acknowledges that the estimation of the first dose in clinical trials is a bad--but it's the only thing we know how to do. So this has got to be better, because it's better than nothing. You know, because right now what we're doing is a very crude approximation.

[Slide.]

What's another application? And--in conclusion--the two-year rodent carcinogenicity study--in mouse and rat. It costs $2 million. It takes at least three years to do. And there's always controversy about the outcomes of these. Yet it has an enormous effect on the drug's marketability.

Is it necessary to do these studies for all drugs now? Can computational methods replace some of them? I'm not saying we're getting rid of all testing. But if we know a lot about a particular compound, based on the experience of the past, perhaps with predictive modeling there may be a subset of compounds in which we don't have to test as vigorously. And those which we know very little about--and the computer can tell you that; that the compound is not covered in the learning set, and therefore you better do all the studies.

But if a compound is another--you know, antihistamine, maybe there's a lesser path because a structure that's so well represented in the data set, that it's sort of silly to keep testing it

over again, just to meet a regulatory requirement.

So we're hoping that this would reduce unnecessary testing and put the resources where they're needed; testing things that we really don't know anything about, and that are new--that are really new compounds.

[Slide.]

So the challenges for accepting predictive modeling: we need accurate, validated--and that's always--you know, what we mean by "validation" is always arguable. But we need to develop that. That's part of our mission.

Standardization of software; experience and training--it's not something that's going to go on a reviewer's desktop ever, because it requires interpretation. It's a really special skill.

We need more databases; adequate sharing of proprietary information; the bigger the database, the better. But we need, also, regulatory mangers and scientists that are willing to consider new ideas--consider; don't have to adopt--consider. That makes a big--you know, opens

the door for innovation.

And then the ned for an objective appraisal of current methods. It's the emperor's clothes. How good, really, is what we're doing now? And that is something that's painful, but it's something that needs to be done. Compared to what? Is it better, worse--compared to what?

[Slide.]

In PhRMA 2005 meeting that occurred several years ago--and I think it was very farsighted--Price Waterhouse Coopers had a paradigm. And they said, "Right now you have primary sciences: the lab-based, patients--you know, clinical trials; and the secondary is the computational--what the call "e-R&D"--that there will be a transition where they'll reverse from primary to secondary. And the primary science maybe in the next generation, will be the modeling and predictive science, and the lab and clinical will be the confirmatory science.

So, with that, I'll end my talk. We've published much of what we've done. A lot of it is

in press right now. We have a web site: our maximum recommended daily dose database is on our website, and a lot of people are working with it, and we're happy to say that they're getting the same results--which was nice.

And I'll end my talk here.

CHAIRMAN KIBBE: i'll take the prerogative of the Chair and ask the first question. And then we'll get rolling.

Your database looks wonderful when you're dealing with toxicity. Have you also done a similar thing with clinical effectiveness, or utility, of compounds? Some way of looking at the structure, and then looking at the effect, and being able to predict how effective one structure is relative to another?

And then follow up with that--if that's true, can we plug into the opposite end of your program and go back the other way, and just bypass drug discovery?

[Laughter.]

DR. CONTRERA: [Laughs.] Well--no fair.

I'll start with the last one--but you'll be only discovering what we already know. There may be--

CHAIRMAN KIBBE: But I was thinking of plugging in different parameters--

DR. CONTRERA: Yeah.

CHAIRMAN KIBBE: --in the toxicity and outcome: lower toxicity, higher efficacy--

DR. CONTRERA: Oh, yes. Yes.

CHAIRMAN KIBBE: --and then go backwards.

DR. CONTRERA: Yes, that's possible.

CHAIRMAN KIBBE: Thank you.

DR. CONTRERA: But getting back to efficacy--yes. In fact--I mean, industry is using it as an efficacy tool all the time. That wasn't our mission. But potentially--certainly applicable. And sometimes we stumble on those things. But that isn't our mission.

And you know where research--we've got four people in this unit. And then we have contractors. And then we get students. So we're a small, tight unit. And you have to be very focused, in terms of your priorities, and doing

what is feasible first, and less--and so we didn't get into efficacy. No.

CHAIRMAN KIBBE: Who have I got down here? I've got everybody on the right side.

So we'll start it at the end, and work our way down.

Go ahead.

DR. SELASSIE: Okay. I have a couple of questions for you.

First of all, with your database, you have in-house data that you're generating for your toxicology?

DR. CONTRERA: Yes.

DR. SELASSIE: Do you ever go to the literature and get information from it?

DR. CONTRERA: Yes. Actually, that could be a much more complicated slide. But we mine everything. We mine other databases; the NIH databases; literature. And, in fact, we're using--we're using our CRADA with MDL--because MDL owns almost every journal in the world now--practically. Elsevier owns almost everything.

And so--and they have access to data that's enormous.

So, using the leverage with a publishing company, we have a pipeline now to the literature. Yes.

DR. SELASSIE: Okay. I have another question.

DR. CONTRERA: Yes.

DR. SELASSIE: When you're inputting the structures, do you all ever use the SMILES notation?

DR. CONTRERA: Yes, we use SMILES. There is some ambiguity. In fact, the software will use either one.

But, the .mol file--you know, you could add a lot more: three-dimensional components and other--you know, .mol file has the capability of doing a lot more than SMILE. But the software will run on both--both systems.

DR. SELASSIE: Okay. And noticed, in using your descriptors, or using the e-state discriptors--

DR. CONTRERA: Yes, e-state.

DR. SELASSIE: Do you ever use log P in there? For partition coefficient?

DR. CONTRERA: Oh, yes--log P is part of the MBL QSAR package. It's also part of the MCASE package.

For carcinogenicity--I will be frank--for carcinogenicity predictions, log P doesn't have any role at all. We took it out because it didn't do anything. It didn't help.

CHAIRMAN KIBBE: Jurgen?

DR. VENITZ: Yes, I wanted to commend you for your efforts. Obviously, this is exactly where the FDA can something contribute that nobody else can--

DR. CONTRERA: Yes.

DR. VENITZ: --because you're in the possession of all this proprietary piece of information, you can perform meta analysis using qualitative methods.

A couple of comments: the first one--right now toxicity is your main endpoint.

DR. CONTRERA: Right.

DR. VENITZ: You're looking for predicting toxicity--

DR. CONTRERA: Right.

DR. VENITZ: --or doses. You might also want to use similar methods to predict biopharmaceutical characteristics, such as bioavailability, metabolic stability, permeability.

DR. CONTRERA: Yes.

DR. VENITZ: Because, I mean, in the sense of the Critical Path method, where you're trying to screen out, in silico, potentially bad candidates--

DR. CONTRERA: Right.

DR. VENITZ: --that's, I think, number one or number two on the list why drugs fail. They don't get absorbed, or they get metabolized.

DR. CONTRERA: Yes, right.

DR. VENITZ: So that if you wanted to use your resources, other than toxicology, that would be one thing to do.

DR. CONTRERA: Right.

DR. VENITZ: The second comment is maybe a

little less--or more farfetched, I guess: and that is to look at things like biosimulations, that don't use empiric models but, rather, mechanistic models to predict what might happen with new chemicals. In other words, you're trying to mimic physiology--and, again, I think is think this is still in the infancy, in terms of predicting certain kinds of--

DR. CONTRERA: Right.

DR. VENITZ: --toxicity. But it may come in handy, in addition to those more statistical empiric predictive models.

DR. CONTRERA: Well, in terms of your last point, with the mechanistic data, that's why we have a collaboration with University of Leeds in England. Because they have an enormous amount of experience with human expert rule-building, and LHASA Ltd. And they have a--their Derek program is used all over Europe for predictive modeling, and that's based on getting data and trying to--and a human committee coming up with mechanistisc rules, based on--and so--but we felt that was out of our

expertise, but it was way--it was exactly what they're doing. And that's why we're developing a CRADA with that group. Because they are probably one of the best, in terms of taking statistical modeling--Bayesian modeling--and teasing out rules--mechanistic rules.

And in terms of the ADME--of bioavailability--you know, Dr. Hussain has already brought that up as a wave of the future, and we actually had discussions with Simulations Plus, and Ray Bolger, to get into that.

But we're going to do that with those people--within our group--that have expertise in that area.

My group is really, mostly toxicologists and chemists. So now we've got--and we don't just leap into a new area until we develop alliances with people that are experts in another field.

DR. VENITZ: One--can I make one last comment?

CHAIRMAN KIBBE: Go ahead.

DR. VENITZ: It's not related to chemistry

as much as looking at biomarkers; and that is relating biomarkers to outcomes--either pre-clinical or clinical outcomes, where you could use similar methods to--

DR. CONTRERA: Yes, I think it can be. This is--you know, this is in its infancy, but I think it's an emerging science. It's great. It's really exploding.

CHAIRMAN KIBBE: Dr. Koch?

DR. KOCH: I just wanted to comment that I think it's a very impressive approach. Will there be a follow-up, in terms of using this type of data as a way to enhance new drug discovery, or some examples when something some together? Or is there a possibility that it actually raises the bar on new drug discovery, because of predictions?

Maybe a suggestion--unless you've already done it--maybe tie in with what Art has suggested--but if you put into that model some already-approved past generation pharmaceuticals--maybe some simple things--

DR. CONTRERA: Yes.

DR. KOCH: --like acetaminophen or aspirin or some steroids--and see how you would have predicted their--

DR. CONTRERA: Sure.

DR. KOCH: --present day efficacy.

DR. CONTRERA: Sure. Sure. To some extent that's part of what we do--what we call our internal validation, where you take compounds out of the system, then you have the system predict them--and not only predict them, but then show you what clusters of compounds that were in the database it used to make the judgment of whether it was going to be carcinogenic or not.

And, actually, that's the most, I think, enlightening tool, in terms of the scientists. Really, it's an interface. What we're tryign to do is develop an automated expert. You know, when you go to an expert, what does an expert do? He says he thinks--he has a good deal of experience, and he says, "You know, I've seen that before in my years of experience." And also, he goes to the literature, and he--and so all we're trying to do

is, to some extent, automate that, speed up that process.

We're still going to have the human interface, but people are so--you know, get a little bit suspicious of the machine, but we're asking the machine to do what we ask our human experts to do. But maybe it can do it a little bit more thoroughly, you know. But you still have to evaluate the output of the machine.

So one thing is good about many of the softwares is that you get the basis for the conclusion. And then you can judge and say, you know, "This doesn't make sense. It says it's carcinogenic, but the top 10--the compounds that it modeled in the cluster of compounds that it used to make the model, none of them are--"--you know. So you say, "This is junk. There's something wrong."

So you still--so you need good trained operators to be able to interpret.

CHAIRMAN KIBBE: Ken?

DR. MORRIS: Yes, thanks. This is really a nice presentation. I think it's pretty exciting.

The first thing an expert tells you, of course, is their rate--by the way.

[Laughter.]

My question actually deals more with mayabe what will be in the future, I guess, because at least as I understand from the presentation, that your descriptors are all based on the molecular structure.

DR. CONTRERA: Yes.

DR. MORRIS: And then responses--

DR. CONTRERA: Right.

DR. MORRIS: --which is the typical QSAR approach.

I guess--and we were talking about this at breakfast this morning--the thing that sort of comes to mind is the opportunity--or is there an opportunity, I guess is the question--to use the targets--that is the receptors or whatever it is that stimulates it, and do a more--what would be a more traditional, I guess, molecular simulations approach to actually backing into--the reason the rational drug design in many senses didn't meet its

promise was because of the statistics, as well as the lack of knowledge of efficacy; whereas here, your same database should give you significantly more data--if you can identify the targets, and if there's--

DR. CONTRERA: The targets aren't necessarily well-defined. And there are better laboratories than us out there that are doing target, you know--modeling targets. And in the pharmaceutical industry, that is their domain.

And what we wanted to do is what no one else was doing.

DR. MORRIS: There are people modeling targets?

DR. CONTRERA: Oh, yeah. Yeah. They have three-dimensional modeling of receptor targets in order to develop drug molecules--

DR. MORRIS: Oh, no, no, no--I don't mean to develop drug molecules.

DR. CONTRERA: Oh, okay.

DR. MORRIS: I mean, to use the database--

DR. CONTRERA: Yes?

DR. MORRIS: --with targets, particularly if you have structures for the targets--

DR. CONTRERA: yes.

DR. MORRIS: --to be able to go back and calibrate this. Because the problem with the people that you're talking about, and the problem they face every day is the vagaries in their force fields, as well as some of the other tools they use.

So, with this as an anchor, so that you actually have the data with which you could calibrate those in a sort of semi-empirical fashion--

DR. CONTRERA: Yes, that may--

DR. MORRIS: --it seems like you'd have a big leg up.

DR. CONTRERA: Yes, maybe there would be a complementary--you know--

DR. MORRIS: Yes--no, I don't think--I'm not saying you should--

DR. CONTRERA: --yes, we stayed away from that type of--but you're right. Yes.

CHAIRMAN KIBBE: Pat, do you have anything?

DR. DeLUCA: Just--certainly impressive, what you're doing. And I guess I'm wondering about applying it to the product development part of drug development, in that once something is, you know, discovered--knowing it's a weak base, or a weak acide, knowing the PKA, solubility--some of those parameters that can be plugged into the database that would then a lot right in the formulation aspects--is there a salt form, if you're looking for a higher concentration that you may not--is not soluble in the form, the weak base; what salt form might be performed, a drug made?

So if the database can help in that product development scheme, to look at formulation aspects, I think that would be very helpful.

DR. CONTRERA: Right. I think, again--that's something we got involved in--I think we get involved with, because I know it's a big problem for industry. It's one of the reasons why drugs fail, in terms of bioavailability and

solubility.

CHAIRMAN KIBBE: Najer--we're working our way around the table. So I don't want to--

DR. SINGPURWALLA: Well, this is not a criticism of you--[laughs]--but it's a criticism of the Price Waterhouse Coopers slide that you put up.

DR. CONTRERA: Yeah?

DR. SINGPURWALLA: I think that slide is very misleading. And I'd be very reluctant to put it up. And it's because of a slide like that that our Chairman raised the question that he raised.

The slide seems to give the impression that computers are going to address these issues, and it's going to make the primary science secondary. Now, the reason why I take objection to this is because of the following: that any model-building endeavor involves three elements. Element number one is the basic science--that's the physics, the chemistry, the pharmacy--whatever have you. The second thing it involves is data, if available. And the third thing it involves is the judgment of the scientist--even in pure theoretical

physics, the judgment of the scientist plays a very important role.

So, what the computer--and then, there is a theory, which helps you put all these together. So there are two theories: there is the theory of the science, and the theory of the fusion--how to put all these things together. And the computer's role is simply to facilitate the putting these three all together.

So I think one should be very careful in trying to highlight the role of the computer here. There is a parallel in what you're doing, and what is done elsewhere, in the context of nuclear weapons. Similar problems are faced.

DR. CONTRERA: Sure.

DR. SINGPURWALLA: We can't talk much about them, but I think you may want to look at what else is going on in that area, and downplay the role of computers, and not use this Price Waterhouse Coopers slide, because obviously they are a consulting firm, and they're going to push computers.

DR. CONTRERA: Well, I don't know--they also are--I imagine, are involved in all kind of research beside computer research. They do everything. They just look at markets in general.

But--and maybe there's--calling it "primary" and "secondary" science, people that are lab-based would say, "Oh, you've made me a secondary citizen" kind of thing. And you can change the term.

All we're saying, that the emphasis is goign to change. There's going to be more emphasis on trying to model and predict; before you spend a lot of money on an experiment you better make sure the experiment's worth doing--or it hasn't been done before. And that's what we've been wasting money for a generation.

CHAIRMAN KIBBE: Marvin Meyer?

DR. MEYER: Have you had any successes yet, where the computer and the software predicted no toxicity, and the agency therefore did not require certain toxicological testing? And I assume the answer is "No, we haven't."

DR. CONTRERA: We--

DR. MEYER: How close are you to that?

DR. CONTRERA: No, we haven't applied it that we. We're very careful about saying that--we're not using this to make a regulatory decision. This is a decision support.

DR. MEYER: But you could.

DR. CONTRERA: But down the road maybe it will be. But right now we're not there yet--by any means there yet.

But right now, it's being used more and more heavily by the pharmaceutical industry, in terms of their screening process. That's where the big role is.

And, you know, it's just like--I don't know if you're familiar with--but when Bruce Ames came out with the Ames test--you know--for mutagenicity, all of a sudden everyone started using it. It was an easy test. It was relatively inexpensive. The drug companies started mass screening of all the compounds. And before you know it--you know, we don't get Ames-positives

anymore in the agency. Whereas we used to get Ames-positive tests that were compounds. They're gone. So that tells you that a testing paradigm could have a big effect.

And so these programs that predict carcinogenicity will filter out those rodent carcinogens that are really--major rodent carcinogens will disappear. And eventually people are going to say, "You know, we've been doing this test. We never get much positive anymore. You think we should--"--that's where I want it to go. It won't happen by fiat, it's going to happen by--but it's going to happen, you know.

CHAIRMAN KIBBE: Judy has a quick one.

DR. BOEHLERT: Yes, Judy has a quick one--going out of order.

When adverse drug experience reports come into the agency, is anybody going back to your database and saying, "Could this have been predicted? Does it look like this is real? Or could this be a fluke?"--you know. "I wouldn't expect it for this molecule."

DR. CONTRERA: They do. Actually, they do come to us. They come to us a great deal when there's ambiguity--in test data, and they can go either way; you know, there's some slight positives in one test, it's like negatives on the other. And they'll use it sometimes, again, to try to come in and weigh on one side or the other. And that's what we call "decision support."

It happens a great deal in the contaminants and degradants area. Now, a compound comes up really late in development--all of a sudden they scale up, and there it's over x-percent that the ICH level, and a company said, "Oh, it's harmless--"--you know. And we say, "I don't know. You've got to lower it."

And then what usually happens--because I was a reviewer for 10 years, and I was a team leader during that period of time. So I sort of came up from the review ranks. And many times a chemist would come running to me and say, "Oh, we've got to do something about--tell me everything you can do, as a pharm tox. What is it? And is it

bad?" And I said, "How do I know?"--you know.

And, you know, you look at it and you say, "Well, is it like something that's real bad?" And then you'll tell the company that they have to do a tet, because you've got to close the regulatory loop. I'd say, "Oh, do a two-week rodent study, and if it's clean you can go on." "And do an Ames test." If it doesn't show a positive, then they could probably go with over 2 percent.

Now, that's an answer, but the chances of getting any positive toxicity in a two-week study is zero to none. And they've already done an Ames test probably, so you do it again.

So what I'm trying to do is have a rational basis for regulation, where you go to the computer, where you do a predictive model; the model gives you 20 compounds that are 90 percent sinilar, and what their regulatory or testing history is. Now, you bring that to a reviewer and you say, "You know, I think there may be a problem because this compound is like a teratogen. It's 90 percent similar to a known teratogen." So now you

can go to the company and say, "Look, either you can reduce it, because we have reason to believe, based on the literature, that it's close to teratogen. But if you don't think it is, do a--"--now I can tell you exactly which test to do. "Do a segment 2 teratogenic study. And if it's negative, you're clear." Or reduce the level.

But I think that's a rational basis of regulation.

CHAIRMAN KIBBE: We need to start to close this up. So--because we've been having lots of fun with this talk.

[Laughter.]

Go ahead.

DR. KARO: Okay. I havea comment, and then two questions.

First, I would take exception to something that you said early on, that we're still using toxicity tests from 50 years ago. You know, as a toxicologist, we've made a lot of progress.

DR. CONTRERA: Sure.

DR. KARO: And there are some new

tests--especially in sensitization; that we're not using the old tests.

The other is that with QSAR, the quality of the database is absolutely essential to know. How do you evaluate the quality of the various databases that you're using?

And, secondly, you mentioned validation. And that is, you know, critical. If you have a human database, how do you validate the predictions from the human database?

DR. CONTRERA: Well, human database validation is probably the--that's the most difficult. And we're not sure yet how to best validate that. We're right now trying to devleop models that are stable, and we validate those by looking at the cluster of compounds on which the decision was based to see if a human expert would agree that they did represent aspects of the test compound that made sense--you know?

In terms of data quality, that's always a problem. And that's why we try to rely on data that's already been screened by committee. In the

case of--that's why--and one of the good things about carcinogenicity data is that we have a carcinogenicity assessment committee within the agency. And the committee meets and decides on what the study said. Because there's a lot of ambiguity within the studies. And so we base it on the calls of the CAC committee--calls in our files, going back many years.

And in terms of other databases, we try to base it on committee-based data sets--you know. Teratology--the tera agonist--there's a lot of organizations that have already, you know, reviewed a lot of this data and have published it.

But often, you know--that is always a problem with data mining. And my bottom line is to predict a performance. Because if there's really a lot of junk in the database, predictive of performance will go down. But if the data set has good predictive performance, then you have somewhat--

DR. KARO: It's primarily prediction?

DR. CONTRERA: Yes, the predictive--and

how we validate, we do it two ways. We keep compounds out. They're never in the learning set--to use later, to see how well it predicts. And also we take compounds out of the data set a little out of time--

DR. KARO: Right.

DR. CONTRERA: --model and then, you know--which is the traditional way QSAR people do it.

DR. KARO: Let me share and experience.

DR. CONTRERA: Yes.

DR. KARO: I developed a model for skin irritation, using a human database--

DR. CONTRERA: Yeah.

DR. KARO: --that, using this internal validation, was at 90 percent predictive.

DR. CONTRERA: Yeah.

DR. KARO: We then went and tested it on humans, and it was like 30 percent predictive.

DR. CONTRERA: Right. And that's what we've always been afraid of. And that's why we use external validations a lot. And that involves--the

best external validations come from--in areas where there's a lot of data--you know? But most of the time people try to put all the data they can find into the model, and then you have nothing to test it with--you know?

But because we're in the agency, compounds keep coming in. So we stopped collecting at a certain point for the database, so we have 1,200 compounds. We wait two weeks--or a year--we'll have 24 new carcinogenicity studies. So we'll test it against those, you know. And they represent new drugs.

And so that's the best sort of real-world kind of testing that we try to do.

DR. KARO: And then you readjust the model--

DR. CONTRERA: Yeah. Yeah. And then we go to the model. And so with our collaborators, we tell them on a yearly basis, we have to give them an updated, you know, software.

CHAIRMAN KIBBE: Nozer is going to get the last word in--I cant see it. And then we're going

to have to move on, or else we'll be here 'til midnight.

DR. CONTRERA: Okay.

CHAIRMAN KIBBE: You're doing a great job. We're really enjoying it.

DR. SINGPURWALLA: Well, the comment is: the new paradigm, you said, is modeling and prediction. I would like to suggest that the new paradigm be fusing of information from dierse sources, so that you get good predictions.

DR. CONTRERA: Yes. Yes.

DR. SINGPURWALLA: I think the focus should be changed.

DR. CONTRERA: Using it from everywhere that you could possible find. And that's where leveraging and collaborations are essential. You cannot do this alone. No one can.

CHAIRMAN KIBBE: Thank you. Okay, thank you very much.

Keith?

DR. WEBBER: The next speaker is Dr. John Simmons, who is the Director of the Division of New

Drug Chemistry I, in ONDC. And because we have to start the open public hearing at 1:00, we may want to consider saving the last speaker--Lawrence Yu--until after lunch, perhaps.

CHAIRMAN KIBBE: Okay, thank you. John?

DR. SIMMONS: Yes, how much time do I have?

CHAIRMAN KIBBE: John's slides are being handed out as we speak. Don't go looking for them. You have one-and-a-half milliseconds. But just go ahead.

[Laughter.]

DR. SIMMONS: I'll try to keep it as focused as possible.

Office of New Drug Chemistry

DR. SIMMONS: I guess, just a little background. You know, the Office of New Drug Chemistry is really where--is the incubator for this journey of change. And we'd like your constructive comments and your input, because we are trying to change some paradigms, and that's not always a clear path.

[Slide.]

I just wanted to highlight four things that I'm going to talk about before I leave. One is the Critical Path Initiative, and where we're at--what our role is going to be; what our current regulatory research is--and I'll explain that a little bit more as we get to it; then, as we look to the risk-based initiatives, as a paradigm for review; and, lastly, what some of our future goals are going to be.

[Slide.]

Ajaz did a very good job of outlining the basic Critical Path components. And, obviously, where our biggest impact is is on that lower arrow. We can certainly step in and help folks that are developing beyond discovery, but all the way up through large-scare manufacturing, and that's going to be our focus, I think.

Likewise, if you look at industrialization, down at the bottom, that's our home; that's where we feel most comfortable. The Office of New Drug Chemistry looks at small-scale

production, manufacturing scale-up, refinement and selection of specifications; and then, finally, large scale. And after that, post-approval changes and refinement, once a product is up and running.

[Slide.]

now, as regulators, and as a regulatory body, and as a person that's been involved in both the research and review and approval of drugs, along this Critical Path, if you looke at some of the areas where we can have a large impact, I'd like to draw your attention to the pre-IND phases. More and more, successful companies are companies that shorten their Critical Path by coming in and talking with us, and meeting with us.

There are invariably questions that can be raised, discussed--scientific issues--that will shorten their journey. And we certainly encourage people to do that.

As you move fruther down the clinical development, once the IND is submitted and the phases start, certainly the end of Phase 2 meeting is probably one of the more Critical Paths along

that Critical Path. And a firm that is wise, a firm that would like to minimize the amount of work that's done over and above what's necessary, would come in to an end-of-phase meeting and meet with all the disciplines--but certainly with CMC.

Oftentimes I see, on a day-to-day basis, oftentimes products that are exciting, that companies are trying to develop in a rapid fashion. Oftentimes their development gets ahead of the manufacturing. And I think this is an area where firms can come in and meet with us, pose questions; we can give some guidance. And I think it helps them.

Another area would be prior to submitting an appliation. There is no way that we can review and approve a new drug application in a short amount of time, unless we have interacted very thoroughly and very intimately with firms along that path. And I think that's something that I always enocourage people to do when I speak at scientific meetings, and gatherings of the regulated industry.

Now, the Office of New Drug Chemistry also gets involved in research--usually initiating research. And I have to be honest with you, oftentimes it's very reactive; oftentimes it's very inefficient; and oftentimes it's very focused.

The Office of Pharmaceutical Sciences has had the foresight to ut in place a rapid-response team, which helps us in that venue. When you're reviewing an application, or you've just reviewed an application, or a problem has arisen post-approval, oftentimes we need to look at scientific issues that the firms simply no longer are interested in--or simply aren't equipped to do, or simply refuse to do. And our rapid response team has done a very nice job of being able to take very focused regulatory projects, put them into place as a research project, report back the findings, and help us make a decision. And that's something that we want to continue to do, but I think we want to do it in a more proactive way; in a way that helps us anticipate, rather than be reactive.

And that's one of the reasons we're here. If you drop down to that last point, I think-- we're seeking your input, we're seeking your guidance. This is a journey that we are embarking on, and I think that's one of the strengths of a committee like this, is to validate and direct.

[Slide.]

Just as an aside, you know we're currently developing new paradigms. The office is reorganizing. We've started a journey where, if you look at chemistry, manufacturing and controls, we are trying to balance CM and C. We've spent an awful lot of time looking at the chemistry of things, and now we're looking more closely and the manufacturing and the control of that manufacturing--as an integral part of this process.

So that is a journey that we're not afraid to take, but it will take some guidance.

We're also looking at a review focus: what should our review focus be? And we're also looking at the research focus: how can the research be focused to help us make regulatory

decisions in a timely way?

[Slide.]

Just to illustrate some of what I've been giving you a prelude to: here are four topics that have involved either regulatory or regulatory research activities. And I'll give you some illustrations after I walk through some of the examples.

Conjugated estrogens--difficult problem for us; complex drug, mixture of actives, not always consistent. We need to look at ways to fully characterize and establish criteria for pharmaceutical equivalence. And we've gone to our laboratory research groups--we've got one in St. Louis and we've got one here in the metropolitan D.C. area--that have been very helpful in that area. And I"ll illustrate that shortly.

Prussion Blue--very recent example of a compound that was used as--is to be used as a counter-terrorist measure; difficult problem to get companies involved with. You know, these are medications and countermeasures that may never be

used, or may only be used in a catastrophic condition. Companies are loath to do all the basic research that are involved in developing those products.

During the review of this product, we looked to shorten the crticial path, and we involved our rapid-response team to look at surrogates--in vitro surrogates--for binding of this particular compound. It's a ferric cyanide compound--a complex salt. It does a nice job of binding some of the radioactive nuclides that are around. And the company that was--the companies that were involved in developing these products certainly didn't havea lot of information, or clinical human experience to go on.

There were issues about the binding capacities, and what impacted those binding capacities. There were also issues of the release of free cyanide. What happens to these compounds upon storage, or use; you know, do we generate toxic--is the cure worse than the prevention.

Inhalation products--another area where

comparing products across products is not always easy, and we invoked our research teams to look at: how do we develop in vitro methods to establish pharmaceutical equivalence? How can we look at particle size, spray pattern and chemical imaging as techniques to help us come up with standards by which we can evaluate these products?

And lastly--and more of a guidance venue--we're looking now at the marvelous combination of drugs and devices. We're looking at stents that are put in coronary arteries. We've got a few on the market already. But in the process of looking at athat it became painfully obvious to us that the roles that the Center for Drugs and Center for Devices played, and how we could interact, needed refinement, needed focus, and needed agreement. And we're working feverishly on some joint guidances so that these products can be approved in a more timely fashion.

[Slide.]

I said I wanted to illustrate a few issues. Conjugated estrogens--when we asked our

research laboratories to get involved in these products, we asked them to look at complex--look at a complex mixture and tell us, in a systemic way, how we can actually measure them.

And the laboratory out in St. Louis did some marvelous work using LC mass spec combinations to do just that. Here is a total ion chromatogram of all the various components.

[Slide.]

And here are some of the individual identities of those particular components. And they can be identified and quantitated. And that helped us in focusing some of the questions that we would, in turn, ask our innovator companies non-innovator companies.

[Slide.]

With respect to the Prussian Blue issue, this was an area that was not too familiar to the center. You know, Prussian Blue is an inorganic therapeutic, and it's been a long time since we've seen inorganic therapeutics in the agency.

We needed to have a better sense of what

to do with things that were largely insoluable; how to look at those, how to evaluate those. So we evoked the laboratory to take a look at them, and they gave us a very nice idea of what to expect when we look at APIs; what types of variations could we see with time, as to binding; what are the batch-to-batch variations--and, in fact, we saw some. And it helped us focus some of the issues that were involved in the approval.

[Slide.]

Likewise, this material can be dried. And, as lots of inorganic salts, oftentimes water is trapped in the matrix--in various matrix holes. And the level of hydration can have a marked difference on the ability to bind a nuclide.

[Slide.]

On to the issue of looking at inhalation products. Our laboratory set up some very nice work that helped us focus what plume dimensions mean to a product; or what spray pattern--how could spray patterns be chemically imaged so that we could look, and compare products across product

lines to come up with some ocnsistent questions to ask firms.

[Slide.]

Now, I'd like to move on to the risk-based CMC review paradigm, and that's something that's a little different than what we've been doing in the past. In the past we've relied largely on the science and the guidance--and by "guidance," I mean guidances that we ourselves have writen, guidances that have been written by international bodies, such as International Harmonization--ICH. We're moving away from that paradigm. We're tryign to move from review by guidance, into review by science and review by risk. And there are clearly some benefits.

To patients, the obvious ones are faster approval of products, increased availability, continued supply. For the FDA, obviously, there's more product and process knowledge; more efficient allocation of resources. If we do risk-based review versus guidance-based review, where does that lead us? And obviously the one thing that

probably is the intangible that is hard to evaluate, and that is the increase in trust and understanding that occurs between companies that are submitting new data to us, and the reviewers and people that approve those products. I think that's an invaluable aspect. If we keep things on a risk and a science basis, I think it's much easier to talk and come to conclusions.

[Slide.]

To industry, obviously it's more efficient and science-based inspections. Now that's an interesting paradigm, as well. Those of you who are from the biologics venue have seen team biologics, where reviewers and investigators go out to sites. We've been exploring that in CDER for small molecules, but not nearly to any organized fashion. And I think you will see that in the future. And I think there's value to that.

There are faster and more consistent reviews. If the manufacturing and the science and the chemistry are looked at in a more balanced way--not only at headquarters, but also in the

field, there's potential for reduced regulatory burden.

The issues of changes and nonconformance requires less FDA oversight, if you draw it to its extreme. We can focus resources on critical issues that way. We can make judgments asto what's more important.

And then there's flexibility on focus as to what's to be done, rather than what can be done. And I think Judy raised that issue. At some point we have to tell people what we would like to see, and that's not always an easy issue to come to an agreement on.

And, obviously, it also improves communication with the agency. You have to communicate with the agency if you want to use a risk-based approach.

[Slide.]

One of the paradigms that our Center Director, at the time--Janet Woodcock, who is now up at the Commissioner level--raised the issue to us was: you know, how do we link quality

attirbutes to clinical performance? How do we link values and specifications to safety and efficacy? And how do we link our inspectional process to those same issues. That's not always an easy line in which to draw the dots.

[Slide.]

Under the new quality assessment paradigm that we're currently lo9oking at, obviously risk-based assessment is high on the list; clinical relevance is high on the list; safety considerations is high on the list.

The process capabilities are also high on the list. At what point do process capabilities become a limiting factor? At what point to process capabilities give us a venue of guidance? One of the problems that often happens in rapid development of drugs is that firms don't have the luxury of making large numbers of batches of things. And I think process capabilities can be used both as a sword and it can also be used as a guide. And I think we're looking toward that paradigm--that guidance paradigm.

The knowledge gained from pharmaceutical development reports--you know, one of the wonderful things about ICH is that we're into this paradigm of sharing information and explaining how you came to the conclusion that this was the optimum formulation. And process development reports are a window into that. And I think we would like to utilize those better as companies move into that paradigm.

And then, obviously, the better utilization of statistical methodologies. Statistical proces control, I think, is a way of the future. I think companies are implementing it in small ways now, but I don't think that firms have had the luxury of developing it on a large scale--at least not the drug industry in this country.

We're looking at assessment, starting from the comprehensive overall summary--something that ICH has given us as a paradigm to look at. At what point can we look to the firm to summarize some of the issues that are involved, rather than us

looking at all the raw data and coming to our own conclusions?

Good review practices, and good scientific principles--current good scientific principles--I think that's probably going to be something you'll hear more and more about.

Increased emphasis on manufacturing sciences--as we move into the new paradigm of the Office of New Drug Chemistry, we are building a manufacturing science team. We're currently identifying and hiring people that have had large-scale, hands-on manufacturing experience. It will be very interesting to see how we incorporate that into the review process. I'm looking forward to it.

The use of critical and peer review of our evaluations--you know, the paradigm up to now has been one reviewer, on review, one product. I think we're going to be working more on a team basis in the future, and I think we're going to be looking at critically evaluating ourselves as to what questions were asked and what decisions were made.

And then, lastly, this integration of review and inspection--I, for one, have always encouraged people in my unit to accompany investigators whenever possible. But there's a different between accompanying an investigator and being an integral part of making the scientific evaluations on that site. And I think that's the paradigm we're moving towards.

[Slide.]

If--my arrows disappeared. What happened?

These are all connected by arrows, but I want to draw your attention to the lower boxes.

VOICE: [Off mike.] [Inaudible.]

DR. SIMMONS: One more click, you think? By George, you're right. Let's see how many clicks it takes.

[Pause.]

Great. Thank you.

Draw your attention to the lower boxes: quality by design, product development report, and comprehensive overall summary--quality summary.

We're looking at those to feed into

risk-based quality assessment, and reduce time review. And, ultimately, if we want to reduce that Critical Path we want to move towards first-cycle approvals--especially when it comes to the manufacturing venue.

We have little control over the toxicity, little control over the efficacy, but we can control some of the manufacturing issues--early on.

[Slide.]

What's in the regulatory future? I think we see increased CMC-only meetings; by that, I mean all disciplines certainly meet as a team with manufacturers, but there are issues tha may involve only the manufacturing, chemistry or controls, in which we can meet with industry and discuss specific issues, to shorten that Critical Path.

Quality by design initiatives; IND Guidances--how can we better help firms formulate what quality we'd like to see, at what levels as you move through the graded phases of development. Obviously, we have to be flexible on things like this. And I think the more information that we

look at earlier on, the better off we'll be. But it puts an awful lot of pressure on industry to develop those data.

Process Analytical Technologies has abeen a driver in the Center. We're looking more and more at looking at in-line, on-line--or at-line--analyses that have feedback loops to manufacturing. We're seeing it more and more.

The integration of review and inspection--I've already talked about that.

Strategies to facilitat first cycle approvals--we'd like your input on that.

Combination products--we're now entering a wonderful world in which devices and drugs are being approved together; where the device is either delivering the drug, or the device is carrying the drug to prevent some secondary impact, as in drug-eluting stents.

Also, with biological-type products--so not that the proteinaceous drugs are within CDER, we can look more closely at biological small-molecule combinations. That's the way

they're used in real life, and I think now we can start looking at them in a more coherent fashion.

Nono-particle technology--where will that take us? How will we evaluate the size and shape and impact of that type of technology on drugs--not only how they're manufactured, but what the toxicity and efficacy of those drugs are. We now have in the pipeline nano-technology products, and they present some very, very interesting questions. And I don't claim to have all the answers, and I'm looking to--I think we're looking to the committee to give us some guidance on things like this.

[Slide.]

Some of our immediate next steps are obviously implementation of the PAT Guidance--Process Analytical Technology. I've had the wonderful opportunity to work with teams of people that we're training to send out to look at these products. You know, we've just come off of a very long journey where we had investigators and compliance officers and reviewers exposed to the same type of information, and trained as to what to

look for when you're looking at process analytical technologies. And I think we're ready to start seeing the fruits of that labor.

Revision of CMC guidances--can we make the guidances more science based? Can we make them more commonsense? Can we make them far less checklist in nature?

Combination prodcut guidacnes--obviouskly that's an area that we have to look at very closely, And this integration of review and inspection--what questions can be asked here? What questions have to be asked and answered on a plant floor?

[Slide.]

I think the two major future goals are: to establish a meaningful regulatory program that's science-based, that supports drug deevelopment and review. I think we're partners in this process. We're not simply a hurdle.

And I think the other one is: to explore regulatory mechanisms to speed that process, or shorten that Critical Path.

So I think I'd like to bring this to a close, and open it up for questions, and ask you to think broadly about some of those issues.

CHAIRMAN KIBBE: Are there any questions for our speaker?

Good. Go ahead.

DR. MORRIS: this is a relatively short question.

I think, when you're talking about the integration of review and inspection, which is a question I get a lot as I visit the companies--

DR. SIMMONS: Yes.

DR. MORRIS: --but is the limitation organizational? Or resources?

DR. SIMMONS: I think both. I think what we're seeing is that in the current paradigm, where there's one reviewer and one application, and one product, scheduling can be a terrible problem. I think, as we move to separating pre-approval from post-approval, and allowing people to focus on developmental and NDA issues, I think we will see more and more structural inspections involving the

reviewer.

I think the other issue is the resources of the field. Obviously, to put two people or three people together at a site requires intense scheduling, the availability of resources--and pre-inspection conferences. You can't go into a plant without a plan.

DR. MORRIS: Yeah.

DR. SIMMONS: And I think that's the type of thing that we're up against. And I think we'll be--I'm pretty confident we'll be able to--

DR. MORRIS: But there's no inhibition to--

DR. SIMMONS: I don't think so. I don't think so. I think it's only limited by our own resources and biases. Yes.

CHAIRMAN KIBBE: Joe?

DR. MIGLIACCIO: Just following up on Ken's question--you talk about what question's asked here, what questions on the plant floor. Remember the scientists who develop the formulation and the process are not on the plant floor.

DR. SIMMONS: Good point.

DR. MIGLIACCIO: So we need--

DR. SIMMONS: [INAUDIBLE] made available.

DR. MIGLIACCIO: Yes. Yes, they are made available. But we have to have a good discussion between industry and FDA about where the division is.

DR. SIMMONS: Yes.

DR. MIGLIACCIO: What questions--

DR. SIMMONS: I agree.

DR. MIGLIACCIO: --are appropriate for the plant floor.

DR. SIMMONS: I agree.

DR. MIGLIACCIO: We don't want to be having detailed formulation discussions--

DR. SIMMONS: No. No.

DR. MIGLIACCIO: --with pharmaceutical engineers on the shop floor.

DR. SIMMONS: No. I agree with that. But on the other hand, I think it--a picture is worth a thousand words. If you're looking at process analytical technology development, you're looking

at the placement of sensors.

DR. MIGLIACCIO: Sure.

DR. SIMMONS: I think there's no substitute for looking and touching those pieces of equipemtn.

DR. MIGLIACCIO: And if I could just make one more comment--you talked about statistical process control--not heavily used. Actually, statistical proces control is somewhat pervasive in the industry. The problem is, the statistics are being applied to data that is being gathered for compliance purposes.

DR. SIMMONS: Yeah. Yeah.

DR. MIGLIACCIO: And I think we're shifting away from that now; that we're now willing to gather data for scientific purposes--

DR. SIMMONS: Right.

DR. MIGLIACCIO: --not compliance purposes.

DR. SIMMONS: Well, thank you--good clarification.

CHAIRMAN KIBBE: Anyone else?

DR. KOCH: John--I know you participated in the training with the combination reviewers and inpsectors. And that continues to come up. And I know it's difficult for the scheduling, but anything that can be done to encourage increased involvement in the training, so that you have more of a base to draw from for setting up the--

DR. SIMMONS: I couldn't agree more. I think there's no substitute for that hands-on experience. I think it's valuable.

CHAIRMAN KIBBE: Anybody else?

If there are no further questions--thank you.

I have logistics question. We have one speaker for the open hearing, and we are at noon. And we have one more speaker that fits with this set. So the question really is: shall we go ahead and run long, and get Dr. Yu done before we break, and come back late? Or do we want to fit him in after the open hearing, before we start the next set?

And what would make more sense?

DR. HUSSAIN: I think the open hearing time cannot change. I mean, that's the restriction.

CHAIRMAN KIBBE: Well, if we have only one person on our list--so.

I mean, if we had an open hearing and the time is used in 15 minutes and we're done, and there's no one else, then we can put him in there.

DR. HUSSAIN: Yes, definitely. Definitely.

CHAIRMAN KIBBE: All right. Okay.

So we will then apologize to our next speaker, and have him have to give his presentation on a full stomach--

[Laughter.]

--which, hopefully, will make him more comfortable.

We will now be at recess until one o'clock. And if the members of the committee will hang around, we'll discuss with you lunch plans.

[Off the record.]

CHAIRMAN KIBBE: I see by the clock on the

wall that we have rapidly approached the one o'clock hour, which means that we will entertain an open-hearing presentation.

Open Public Hearing

CHAIRMAN KIBBE: Dr. Saul Shiffman? Please identify yourself.

DR. SHIFFMAN: I will do.

CHAIRMAN KIBBE: And then you can go ahead and do your presentation--appreciate it.

DR. SHIFFMAN: Well, thank you for your time. I'm just going to take you on a brief excursion to some fairly different territory than what you've covered this morning.

[Music.]

My name is Saul Shiffman. In my day job, I'm a research professor of pharmaceutical sciences, psychiatry and psychology at the University of Pittsburgh.

Ooop--but today I'm here as Chief Science Officer of invivodata, inc., which provides clinical diaries for--electronic diaries for clinical trials.

And, in a sense, I want to shift the focus for a moment from the focus on drug discovery, screening and manufacturing, to the testing of drug products and devices in human clinical trial; and also, in a sense, to shift from the sort of ambitious initiatives considered under the Critical Path Initiative that require new science, new technology, new regulation, toward an example of some of the kinds of things that can be done with current science, current technology, current regulation.

So--briefly, I'm going to talk about the use of diaries in human clinical trials, and the different methodologies that are in place, basically talking about the fact that paper diaries, which are in wide use, have serious both scientific and regulatory, as well as operational problems, whereas newer technologies fall within the regulations and solve these operational and scientific issues; and that the FDA can facilitate the development of those newer methodologies.

So, briefly, stepping back--while

obviously many clinical trials are run with hard, biological endpoints, it's not uncommon that key endpoints are what are call "patient reported outcomes," either because they're subjective states--such as pain, which can't be gathered any other way--or because the patient is often, if you will, the most privileged observer to report on certain events which are objective, but which the patient is in the best position to observe.

[Slide.]

And, in fact, patient report outcomes are collected in nearly three-quarters of all trials, across all four phases of drug development. An FDA audit showed that they were present in about a third of NDAs. And diaries, in particular, are used in about a quarter of trials. And, of course, the function of diaries is to get the data in real time in order to avoid the pitfalls of recall.

The traditional method has been a paper diary. And if you've ever done a diary study, this may bring back some memories. Operationally, there are a lot of issues. Diaries often contain errors.

They're often illegible and therefore, on both accounts, fall under the regulatory standard as a problem; but also operationally, in trials containing diaries, the diary is usually the last source of data that's processed. And so it becomes literally the item on the Critical Path that slows completion of the diary.

A number of academic groups, as well as industry providers are providing electronic diaries, and audits show that they reduce errors and the need for data cleaning very dramatically--by 98 percent--because of the ability to filter the data at its source, and therefore provide operational efficiencies.

But what's important is the potential for the diaries also to provide enhanced validity. And, really, the biggest concern about paper diaries has always been that they're not completed in a contemporaneous way. Anyone who's ever done a diary study has probably seen patients filling them out in the parking lot, or in the waiting room. And, in fact, the field has coined a phrase of

"parking lot compliance."

That's been anecdotal. Let me show you some more formal data.

[Slide.]

We did a study with pain patients. This shows you the data that's usually available from a paper diary. And it shows that the patients returned the diary cards reflecting that 90 percent of the diary cards had been completed in inappropriately timely way. And the problem is that all we have is--in other words, this is what was noted on the card.

The innovation in this study is that we had developed an electronically instrumented paper diary that, with photosensors, made a record of when the record was actually filled out, so that we could try and verify the patients' report of timely compliance. And the data were rather dramatic--which is that if you look at the actual records, only 11 percent could conceivably have been filled out at the appropriate time; in other words, 79 percent of the returned records were

either inaccurate or falsified.

Importantly, we observed hoarding, which is to say on one-third of all days, the diary wasn't opened the entire day, and yet 96 percent of the diary cards were returned for those days.

What we never expected to observe, but did observe, was forward filling; that is, that patients would--

[Laughter.]

--today, on Tuesday, fill out their reports for Wednesday, Thursday and Friday. It made me think that I wanted to stock advice from these folks--

[Laughter.]

--since they could tell the future.

So, clearly, there are very serious problems that go both to meeting the regulatory standard--accuracy and contemporaneous completion--but also, as you'll see, go to the issue of scientific validity.

And, in contrast, we had a group that had been assigned to use an electronic diary. And, in

fact, they completed 94 percent of the entries in a verifiably timely way. So there is a solution to this problem of diary completion.

So what is the benefit, then, for clinical trials of improving the methodology?

[Slide.]

And, if you will, the hypothesis--the compelling hypothesis--is that by getting data in real time you reduce error, which makes trials statistically more efficient, with greater power, and therefore you have both more efficient--that is smaller--trials, and essentially more reliable trials whose answers can be relied upon better.

And, in fact, to try and validate this, a couple of groups have done analyses comparing paper and electronic diaries--of the same phenomenon; essentially parallel studies.

[Slide.]

And what you see is, in fact, a one-third reduction in error variance; essentially a damping out of the noise, which translates into roughly a 50 percent decrease in the sample size required for

those trials.

So this improvement in measurement can produce smaller trials, more reliable trials, and possibly fewer trials, in the sense that trials are often re-done because the first one failed.

[Slide.]

So, in essence what we have here is a situation where the science, the technology and the regulations are already in place. You may not be familiar with ALCOA--it stands for "attributability, legibility, contemporaneousness--"--I forget what the "O" is--and accuracy. So, essentially, there are the existing standards, but they haven't been applied very systematically to diaries.

[Slide.]

So, what is needed? Really, what's needed is not new regulation, but for the FDA to apply its existing regulations in a consistent way. At the moment, some of the older technologies are getting a pass on the regulations, in terms of accuracy, originality, all of those criteria that the FDA has

set. And essentially, it's not so much that FDA has in any way ruled out electronic diaries, as it has left room for FUD--is "fear, uncertainty and doubt." Industry regulatory folks are not known for being adventurous. And so without clear statements from the FDA of its own policies, this has hampered the methodological development of the field.

[Slide.]

So, essentially, as I've said, there's now not just anecdotal but quantitative and formal evidence that paper diaries fail both to meet regulatory standards and scientific and statistical standards; that methods are available, and what is needed, as a small step available today, is for FDA to speak clearly about its interest in newer methodologies.

[Slide.]

The issue of innovation has been with us for a long time. This is a statement from a scholarly journal you'll be familiar with: "That it will ever come into gneral use, notwithstanding

its value, is extremely doubtful because its beneficial application requires much time and gives a good bit of trouble, both to the patient and practitioner, and its foreign to our hats and associations." This statement was made in the London Times, in 1834, and it referred to the stethoscope.

So, initially, most innovations are resisted, simply out of inertia. And I think part of the Critical Path Initiative has to be for the FDA to facilitate the adoption of improved methodologies.

Thank you very much for your time and attention.

CHAIRMAN KIBBE: Thank you.

Anybody have any quick questions--clarify the information?

Marv?

DR. MEYER: Two questions: one, do most of the electronic diaries have a provision for an open-ended response, or an adverse event that isn't in the database?

And then, secondly, coming from the great state of Florida--

[Laughter.]

--where I see a great hesitancy to launch into this modern electronic voting--they much prefer having paper--

[Laughter.]

--do some of the recipients of this device that are participating in a study have resistence?

DR. SHIFFMAN: Let me take the questions in turn. The diaries can have provisions for open-ended text. And, literally, you can use handwriting and record the visual image; or, more commonly, you can provide a little keyboard, and people can type small comments. It varies with the protocol whether that provision is made available or not.

And to, in essence, amplify what's behind your question, sometimes, indeed, one of the reasons paper diaries are so messy is that people write marginal notes, and a few of those have some clinical relevance. You'd like to be able to

capture those, as well.

In terms of patient resistence, that's really been very little of an issue. I showed you the data from this pain study. We replicated those data in a COPD study, where the average age of the patients was in the 60s, and we've done a study of medications for prostate cancer, with average age in the 70s. And, in general, we get not only good acceptance, but, if anything, we've done analyses to show that the performance of older patients is actually better.

So I think we have a bit of ageist bias, thinking that this is only going to be for teenage computer nerds. But there's just a lot of evidence that this is well accepted and well used.

CHAIRMAN KIBBE: Okay. Well, thank you very much.

MS. SHAFFER: Thank you.

CHAIRMAN KIBBE: We now will finish up our morning's activities.

Lawrence is ready to give us his 25-minute presentation in 12-1/2 minutes--to show you the

level of efficiency, when we apply PAT to presentations.

DR. YU: I think I have 45 minutes, right? Until two o'clock. [Laughs.]

CHAIRMAN KIBBE: I do have a priority button.

DR. YU: Okay. I've got it.

After 15 years' graduating from Ajaz, I guess I still look at his students.

Good afternoon, everyone. Chair and members of FDA Advisory Committee for Pharmaceutical Science, and my FDA colleagues and distinguished guests, it give me great pleasure and privilege this afternoon to discuss with you FDA's Critical Path to medical product development opportunities to generic drugs.

[Slide.]

As discussed this morning, the FDA's Critical Path encompasses three aspects, namely:

safety, efficacy and quality.

I want to emphasize that the path to new drug development does not end with the approval of the NDAs, but it continues with monitoring of post-approval changes, post-approval manufacturing optimization, and eventually the development of the generic drugs. In fact, the generic drugs is an integral part of the USA health care system, as pointed out by our President Bush, on his October 8th second Presidential debate: "Tahere are other ways to make sure drugs are cheaper. One is to speed up generic drugs to the markeplace, quicker." So U.S. government looking for generic drugs to limit increase in drug price, while our fellow friends--American consumers--looking for access to low cost, high quality, efficient, same efficacy, and same safety, generic drugs.

[Slide.]

So let's back to the Critical Path Initiative, as Janet Woodcock pointed out--which you saw this slide in the morning--the FDA's Critical Path Initiative is "A serious attempt to

bring attention and focus to the need for targeted scientific efforts to modernize the techniques and methods used to evaluate the safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture."

So, when we apply this to generic drugs--let's define what is a generic drug.

[Slide.]

The generic drug is basically a therapeutic equivalent to a brand-name product. So it would equivalent is defined as a pharmaceutical equivalent and bio-equivalent.

So in more term, is a generic drug is a comparable to a brand-name drug products in dosage form, strength, route of administration, quality and performance characteristics and, finally, intended use.

[Slide.]

When the Critical Path Initiative defined the safety, efficacy and quality as applied to generic drugs, we define as bioavailability, bioequivalence and quality. As you know, that

generic drugs not only should high quality but, more importantly--equal importantly, you know, make sure they're equivalent in terms of pharmaceutical equivalent and bioequivalent and eventually therapeutic equivalent to brand-name products.

So, therefore, my talk covers the following three aspects:

[Slide.]

Bioavailability and bioequivalence modeling and prediction; bioequivalence of locally acting drugs; product design, characterization and in vitro performance testing.

Now let me talk on the first topic: bioavailability and bioequivalence modeling and prediction.

[Slide.]

Now, this is the sketch which I made a couple years away for my talk with Gordon Research conference. At this time I swear I think I invented new term: e-ADME. One time actually I asked my son to register e-ADME as a website, end up like the web site was registered 24 hours ago.

So I lost that opportunity to register web site for e-ADME.

The basic fundamental is connect with your control this morning's talk is the e-R and D--e-research and development. Here, ADME means "absorption, distribution, metabolism and elimination." So basically e-ADME is electronic ADME.

In terms of predicting bioavailability and bioequivalence, or bioavailability--if you look at the approaches of predicating forecast the bioavailability, bioequivalence, there's two approaches to get there. One is experimental approach. You measure solubility, you measure permeability, you measure metabolism, you measure protein binding, and you measure many, many others as development scientists did in their discovery stage.

From those pharmaceutical measurements, you select the so-called pharmaceutical leads. The leads will be--a number of select leads will go to animals, hope from animal models to predict

bioavailability information for humans.

Now, another approach--which I will highlight here--is computer modeling approach.

I use red here--biopharmaceutics classification system; compartment absorption transit model--or CAT model--and quantitative structure bioavailability relationships. Now this--I put this slide basically as those research is going on in FDA, by no means incompatible, because we know, for example, in this slide we did not include one of the very well known approaches from Pfizer, and in this case Rule 5.

So let me go through each one of them very briefly--with I think Dr. Jugen Venitz discussed this mornign.

[Slide.]

First, look at he biopharmaceutics classification system. The biopharmaceutics classification is a scientific framework to classify drugs based on solubility and permeability. These two parameters--solubility and permeability--each parameter has two levels, you

end up with four classes, namely: class BCS Clsss I, Class II, Class III and Class IV. Class I is highest solubility, high permeability; Class II is low solubility, high permeability; Class III is high solubility, low permeability; and, finally, Class IV is low solubility, low permeability.

Four years ago, in 2000, the FDA issued a guidance to waiver of bioavailability, bioequivalence studies for highly soluble, highly permeable drugs--those rapidly dissolving, immediate release dosage forms. With issuing the guidance, does not necessary mean investigation research within FDA stopped. In fact, we are continually exploring possible bi-waiver extensions for BCS Class III drugs, namely high solubility, low permeability drugs; we're investigating the effect of sepins on absorption. We're investigating transporters--for example, p-glycoprotein transporter absorption. We're investigating refinement of the BCS classification system.

So research is very active within FDA, as

is shown here. We have three publications so far for this year alone.

We blieve the biopharmaceutics classification system not only its utility in regulations, but also has its utility in drug discovery and development. This is because the BCS system can help you to select a proper dose form; can help you design a formulation; can help you to see what could be issue down the road in the development process.

[Slide.]

So, let's move on to next topic, which--next, the model, is what we call the "compartmental absorption and transit model." Now this model has become a software which was mentioned this morning, called "Assimilation Plus." I have a disclaimer: I have no financial tie whatsoever with Assimilation Plus."

This is a basic software based on this CAT model, which originally developed by myself long, long time ago at the University of Michigan, under professor Kodio Miro.

This basically, basically as a mechanistic model, describes how a drug gets into the blood; how much it gets into the blood; and how fast it gets into the blood. So it's considering the impact of gastric emptying--for example, after lunch, gastric emptying time's probably four hours. Before the lunch, only 20s and half hours. We look at--we incorporate the effect of the small intestine transit time, blood flow, volume, dissolution, permeability, metabolism, distribution and conventional pharmacokinetics.

The research going on is continue to identify critical bioavailability or bioequivalence factors. For example, if you look at this beautiful suface here, on left side--or right side--this is what we call the "Surface of preferable properties as a function of solubility, permeability, hepatic clearance and potency." Now this is surface of purely calculated, based on computer model, basically give you some idea what potentially bioavailability will be for a new molecule which just even have not been synthesized,

based on the solubility and permeability and hepatic clearance you get some idea what to the degree of bioavailability of the drug itself, of a compound above this surface--above this surface. This means that bioavailability will likely below 30 percent; below the surface bioavailability will likely higher than 30 percent.

Now this is the calculate of the theoretical model has not been validated. We are planning to use FDA data to validate this surface for the benefit of the public health.

[Slide.]

The next--the slides basically show you the quantitative structure bioavailability relationship model. Now this model, if you look at the top left, that's basically is the structure and bioavailability relationship. It's based on 691 drugs whose human bioavailability actually is available within the--in the public domain. If you look at structure at the activity relationships or bioavailability versus structure, you've got a correlation coefficient .71. Now, if you look at

it statistically, that's .71 very low.

Now, we look at these 691 compounds--this model--to predict the drugs which were approved around 2002, which we have 18 drugs. These 18 drugs never been utilized to QSBR models. The correlation coefficient is 0.62.

Now if you look at the bottom--look at the rat and dog, how animal predicts human? The correlation coefficient for rat is .41, while the correlation coefficient for dog is .43. So this I can--for this system, for this drug--for those drugs which were evaluated, the computer model at least will not be worth at all than the animal model.

Now, if you look at the bottom two figures, you will say, "Lawrence, you ought to have a five or four points. Why was that?" You say, "N=18." Very simple: because we use 18 data from NDA jacket internal FDA database to verify this model, but those data were not available in the public domain, in the public literature. That's why we say FDA's in unique place to do modeling

work, which we have the data that we believe probably no one else has so complete database as we do.

Well, we're unique place to develop models for the benefit of the public

[Slide.]

So, to summarize, the bioavailability and bioequivalence prediction--we discussed the biopharmaceutics classification system. We're continue investigating the bi-waiver extensions; we're exploring classification refinement. We are continue investigating the impact for transporters, such as the p-glycoprotein impact and absorption, using compartmental absorption and transit model. We use the QSBR model is a quantitative structure bioavailability model should be developed. Unfortunately, at this point, has not been widely used. We believe FDA is in unique position to do this work for the benefit of the public.

[Slide.]

So now let me move on to next topic, it's the bioequivalence method for locally acting drugs.

We all know the bioequivalence method for systemic drugs is well understood, well developed, well utilized. In fact, luckily, we have used them for generic drugs over 7,000, the drug products. However, well understood, well established, well used for systematic drugs does not necessary mean is well understood, well established, well applied for locally acting drugs. That's key scientific challenges, we believe, for those--can be best used off of FDA's Critical Path Initiative for the benefit of the public.

The key scientific challenges include the following: topical dermatological products; nasal spray and inhalation; gastrointestinal, vaginal and ophthalmic products. Now, those products, because a lack of the bioequivalence method--the bioequivalence method often requires the clinical testing, the clinical evaluation. The target of research is to provide a scientific basis for in vitro and in vivo bioequivalence method.

[Slide.]

Let's look at--give you example why is

clinical studies sometimes an issue. Now this is for topical products--I'm sorry, what I want to say is for locally acting drugs, why this issue here? This is because for systematic drugs, the plasma concentration usually relates to the safety and efficacy of drugs, while for locally acting drugs, the plasma concentration is not usually relevant to local delivery of bioequivalence. Because of that, we have to rely on other alternative methods; for example, pharmacodynamics method; for example, in vivo clinical comparisons--for example, in vitro comparison and certainly any other scientifically sound, well established method, which we think is appropriate.

[Slide.]

So, as we discuss here, the clinical method--clinical evaluation is always available for establishing bioequivalence. The question comes back why this is an issue here. Why? What's going on?

Let's look at give example here. This is a topic product. If you look at the cure rate,

different, if you look at the test, in the figure you have n=number of subjects--in fact, the number of patients. So 90 percent confidence interval between test, and reference and cure rate have to be plus and minus 20s. Now, clinical evaluation usually has large variation. In this case estimated variability is around 100 percent.

Look at the table, in the center. Utilize 463 subject; even with 463 subjects used, the confidence interval is minus 8 and plus 20. It barely pass; barely pass. Now if this is 400 subject, this study will fail. In fact, we were told the many clinical trial studies fail because improper power; inadequacy of the human subjects.

So that, in sumamry, for clinical trial studies to document bioequivalence present tremendous challenge for us; tremendous challenge to the industry; tremendous challenge--certainly difficult for consumers because the availability or lack of availability of appropriate scientific, reasonable bioequivalence becomes a barrier to generic competition; become a barrier, in fact, for

process improvement, for product improvement, for products optimization because many cases those changes require documentation of bioequivalence method--of reasonable, simple, scientific front, bioequivalence method is not available and it will be difficult to make any improvement or significant changes.

[Slide.]

As we see here, clinical endpoints have high variabilities, and we hope--we hope, here--develop scientifically sound, reasonable, simple bioequivalence method to reduce unnecessary human evaluation, or human testing.

So this is the developed for the discussion of bioequivalence of locally acting drugs. Let me move on to the topics which are also dear to our heart in the Office of Generic Drugs: product design and characterization.

[Slide.]

I said it before. The generic drugs not only show high quality, but also equally important to show equivalent- to the brand-name products or

we could pharmaceutical equivalence--pharmaceutical equivalence, this means the same drug substance, same dosage form, same route of administration. So, with respect to to "same drug substance," we need to document that exactly same; for example, we have lots, lots issues before with pharmaceutical solid polymorphism. This issue is resolved. But issues still can exist for complex drug substance.

For topical dosage forms, sometimes it's difficult to define whether it's ointment versus cream. So this also presents challenges. So it's exceeding--in factors of the classification dosage form, if those exceed being inside the classification dosage form, how do we see they're the same?

So, therefore, when you define, you give a very clear definition what is called the dosage forms.

And product quality--when your product quality standards; for example, adhesion tests for transdermal products--of course, appropriate scientific, predictive, in vitro adhesion test not

only can be applied for generic drugs, but also can be applied for innovator brand-name products.

Equally important, we need standards for nasal and inhalation products and a novel drug delivery system, such as liposomes, which was mentioned by Dr. John Simmons this morning.

[Slide.]

Another typic that research--the topic I wanted to mention is product performance evlauation. Now, in vitro, dissolution testing has been around for decades; has been very successful; has been utilized for ensure the product quality--give example, left figure, this in vitro, dissolution testing has been around for decades; has been very successful; has been utilized for ensure the product quality--give example, left figure, this in vitro dissolution method can usually predict, for example, polymorphic change; the top one polymorphic 1, the bottom is polymorphic 2. So proper dissolution testing ensures the product quality, able to detect the inadvertent changes of pharmaceutical solid

polymorphism.

Nevertheless, it's a very simple system--just compare to human gastrointestinal tract. You have stomach, you have duodenum, you have jejunum, you have ileum. The volume changes back and forth, in and out. There's 14 leaders in and out. There's different pHs, from 1.4 to 2.1. Before the lunch, average pH is 1.4, 2.1; now after lunch average pH is 6, or 4.5.

Look at the duodenum or jejunum--also more complex is the transit time is changed. Sometimes the gastric emptying time is only two or five minutes, under fasting conditions; sometimes hours.

The fundamental message here is: dissolution is very simplification of a human gastrointestinal tract. That's part of the reason why the very easy, we see the criticism say that dissolution is underestimating, overestimating, and in vitro, in in vivo dissolution methods is formulation-specific. So on and so forth.

So how do we get from here?

[Slide.]

The dissoluation method, beginning was used for quality control, lately has been for in vivo evaluation, basically the dissolution test as a product quality-control tool to monitor batch-to-batch consistency of drug release form of product.

It also has been used in vivo performance testing as in vitro surrogate for product performance that it can guide formulation development and ascertain the need for bioequivalence tests.

[Slide.]

When we look at complexity, for quality control tool, you want to have a simple dissolution test you can use every day for every batch. However, those simple tests for quality control may not be appropriate for in vivo systems. That's part of reason why, where, at the beginning, we're asking to ourselves if these two objectives are consistent? If it's not, we need investigator--when you develop a bio-relevant dissolution method it's predict in vivo--I want to

say it again, dissolution method has been here, has been very successful ensure the high quality for consumers, but those dissolution methods may be over simplification of in vivo system. That's part of the reason why we believe in make an effort to develop bio-relevant in vitro dissolution method to be predictive of in vivo dissolution, to be predictive in vivo phenomena going on in complicated system.

[Slide.]

Before concluding my talk, I want to say a few words on process identification, simulation and optimization tools. You have heard enough--that hisotrically, pharmaceutical products involves the manufacture of the finished products using batch processes, followed by excessive laboratory testing and analysis to verify its quality.

However, the process identification, simulation, and optimization tools need to be developed for pharmaceutical batch processes so that any manufacturing process failure can be readily identified and corrected. When this

process means that a formulation has been defined--has been selected. The product quality ought to be assured by high quality of starting materials, robust manufacturing processes, and limited--not excessive--laboratory confirmation and test or analysis.

[Slide.]

So when we're look in future, the Office of Generic Drugs wants to continue--all go to continue building world class scientific expertise in predicting bioavailability, bioequivalence and process optimization. We face many, many challenges. We prioritize scientific efforts. We will pursue collaborations. We cannot do it by ourselves. Within FDA, we have Office of Testing and Research. I think this afternoon it's the Division of Pharmaceutical Analysis, Cindy is goin to give a talk. She is providing a lot, lot of support to Generics, and office of OTR--also, rapid response teams.

We had a collaboration already in place with academia--for example, University of Michigan,

University of Kentucky, Ohio State University, University of Maryland, and Colorado School of Mining.

We also have a collaboration in place with National Institute of Standard Technology, while pursue collaboration with other government agencies. Finally--not least--with industry.

With that, I conclude my talk. Any comments are welcome. Thank you.

CHAIRMAN KIBBE: Marvin?

DR. MEYER: Lawrence, two questions on that slide on page--I guess it was slide 10, the QSBR model. One--simply, you said you illustrated the one down on the right-hand corner, I guess, as illustrative of the FDA's problem in presenting data publicly. And you had four data points shown from an n of 18.

I wonder why--how revealing would be the other 14 data points, if you're just plotting percent f, human percent f dog? I mean, I have no idea whether you're talking about aspirin or you're talking about vitamin B-12.

DR. YU: Well, I guess, first of all, Marvin, you have to believe me what I said, here. [Laughs.]

DR. MEYER: Okay. [Laughs.]

DR. YU: Secondly, in this indeed is very simplification modeling, and I can show you slides with actually 18 drugs--their specific name--

DR. MEYER: Okay.

DR. YU: Those 18 drugs were approved in 2001 and 2002. The human bioavailability data for all those 18 drugs were available, actually in public domain--the majority either from the Physician Desk Reference. However, for animal data--for example, if you look at rat, we only have--I only was able to find five drugs whose animal data--rat bioavailability--that were available in the public literature. The rest--basically, that's 13 drugs--were not available in the public domain.

DR. MEYER: My statement really deals with agency paranoia, is: why can't you show us the data points without saying, "This is a Pfizer

product, this is a Lily product, this is a Teva product." Just say, "These are products that are marketed." Or "These are analgesics." Or "These are antihistimines," or--

DR. HUSSAIN: I think the key is this: the animal data may not be in the public domain. The human data would be on the label and so forth.

So if you are able--if you can trace back what the drug was. That was the reason.

DR. YU: If I showed all 18 drugs here--

DR. MEYER: Mm-hmm.

DR. YU: --basically, I disclose all the animal data, because you're able to see it. And then--

DR. MEYER: But if you don't tell me what the drug is--

DR. YU: Yes--

CHAIRMAN KIBBE: You're obviously not a lawyer, Marv.

DR. MEYER: Oh, okay.

[Laughter.]

DR. MEYER: I'll pass on that.

The second question--

DR. YU: I guess I don't want to get myself in trouble.

DR. MEYER: Yeah, I know--well, that's paranoia, isn't it.

[Laughter.]

CHAIRMAN KIBBE: It's only paranoia if it's unreasonable fear.

DR. MEYER: Yeah.

DR. YU: Marvin, you're SG, you can see all this data.

DR. MEYER: Well, then I'll have to be quiet about it. So I don't want to do that.

[Laughter.]

CHAIRMAN KIBBE: And that's really hard to do, too, eh?

DR. MEYER: Maybe a less philosophical question: if I look at the upper left and the upper right, and I draw a line at, let's say, 70 percent f--on the y axis--

DR. YU: Mm-hmm.

DR. MEYER: --I have a range that goes

anywhere from 30 to 100 percent, as experimental or observed--in both cases.

DR. YU: Mm-hmm. Mm-hmm.

DR. MEYER: So even though the r-squared may be acceptable, I say you don't have very good predictability--at least at that level of percent f, which would be one of interest I would think--70 percent.

DR. YU: Marvin, you have--indeed, you have an excellent question.

DR. MEYER: [INAUDIBLE]

[Laughter.]

DR. YU: I guess I can answer it two ways; twofold.

First of all, that's part of the reason that the quantitative structural relationship, as I stated, that the FDA follow in Biologics meeting, follow-on protein biologic product meeting that one professor expert state, it's unrealistic at this point--maybe in the future--as you also point out this morning, the QSBR alone--alone--can be provide for regulatory decision-making. In other words,

quantitative structure activity relationship will be used for supportive information, but however cannot provide a conclusive data for regulatory decision-making--at least today.

DR. MEYER: There's kind of a line between--I tend to agree, it's maybe better than nothing--maybe. But if I were in a company, and I went to management and I said, "Well, I can predict the experimental bioavailability," and my vice president says, "Well, what will it be?" "Well, somewhere between 30 and 100 percent."

[Laughter.]

I better start looking for another job, I would think.

DR. YU: Actually, if you look at it, when you place 100 drugs--supposedly, at this point, you have 100 compounds. You have $1 million. The job is: give me maximum information you can with this $1 million. No, 100 drugs you're available, you can blindly pick up 100 compounds, you pick let's say 10, for example, for human evaluation--okay? And then probably a couple of them--for example,

the bioavailability is 0 or 5 percent, so you failed. So at least failure rate, instead of you--your test, you got a 7. However if you use computer model, you pick the 10 with $1 million, likelihood you got nine. You're getting a lot with this simple computer model, you're only cost $10,000 versus $1 million, you benefit tremendously.

CHAIRMAN KIBBE: I think we have some comments on that.

Ken? And then Nozer.

DR. SINGPURWALLA: I would like to pursue this slide, and the previous slide. So why don't you put up number nine first, please?

DR. YU: Okay. Please.

DR. SINGPURWALLA: I'm a little intrigued with it. You have four variables: surface permeable properties as a function of solubility, permeability, intrinsic hepatic clearance, and potency. You have, actually, five variables, and you're portraying them in two dimensions.

So I don't know what's the purpose of that particular illustration. I don't get a sense of what it is supposed to convey.

And the second point is: irrespective of my first point, what was the basis of your computer models? A computer model is based on some theory, or previous data, or a combination of it. So it's not clear to me what is the basis of that model?

DR. YU: Well, I'll try and answer the question.

This bsis of the computer model is a mechanistic model--okay? If you look at absorption, you basically have four fundamental processes going on. One is gastric emptying and the intestinal transit; second is the dissolution; third is permeation across membrane; fourth is metabolism. So this model consists of about 100 differential equations encompasses all these processes going on. Is basically what we call the physiology model.

And this physiologic model--if you look at the key parameters impact those mathematical

equations--you have solubility, you have permeability, you have clearance, and you have dose. So the reason important your dose is here, because how much input into the body will impact the dissolution.

Now, another I think important terminology is bioavailability. So, basocially, bioavailability is a function of solubility, permeability, hepatic clearance, and effective dose. Of course many, many other factors, but here, simplification is basically theses four, five--four basically are fundamental parameters which ipact the bioavailability.

So, therefore, when you look ata those four parameters, if you know effective dose, the potency, your educated guess, if you look at this surface, you get some idea what likely bioavailability will be in humans before you even actually doing it.

So the advantage is the same for the early stage that leads to selection. If you have a huge number of subjects--which when I gave my--I say

100--in fact, we have 1,000, for example--the candidates for human evaluation. You need to--for human evaluation which one you select? So this surface will help you, which one has a likelihood to be successful--likelihood to be success.

DR. SINGPURWALLA: But you have three variables labeled--

DR. YU: Mm-hmm.

DR. SINGPURWALLA: --so this illustration only pertains to three variables. And you said you had five variables, and a hundred differential equations.

DR. YU: It was--yes, we have a hundred--the way--do have a hundred differential equaltions. But a differential equation is a key parameter here is solubility, permeability and hepatic clearance--and dose. That's why I say dose is 1.0. In fact we have a series plot--for example, dose 0.1, 0.5, 1.0, 5 and 10--a--plot. So when you select a specific dose, and then you look at this plot, and this plot--you have three parameters, basically--solubility, permeability and

hepatic clearance. And then from there you see which is more appropriate candidate for human evaluation.

DR. SINGPURWALLA: I think I made my point. You see three variables here. There are two others--I'm sorry, three parameters here. You have two other parameters. You need another picture to connect these with those. And I won't pursue the matter.

Let's go to number 10--

DR. YU: I think this talk about hours, all the mathematics from one stepwise.

DR. SINGPURWALLA: No, there are certain principles.

DR. YU: Yes.

DR. SINGPURWALLA: You can't show, in two dimensions, more than three dimensions.

DR. YU: Okay. Thank you.

DR. SINGPURWALLA: All right.

Number 10--picture number 10.

DR. YU: Okay.

DR. SINGPURWALLA: Now, you know the

correlation coefficient, r-squares--

DR. YU: Mm-hmm.

DR. SINGPURWALLA: --only measures a linear relationship.

DR. YU: Yes.

DR. SINGPURWALLA: You could have two dependent variables that are non-linear--

DR. YU: Mm-hmm, mm-hmm.

DR. SINGPURWALLA: --and completely dependent on each other, which r-square doesn't capture.

So, I go back to the point raised by Marvin, here--and previous people. There are only four or five points. They don't look linear to me at all. And you can't claim a correlation--you can't claim any meaningful correlation of point .43. It doesn't have any meaning.

DR. YU: Actually, you made excellent point. I guess I did not make it clear in my presentation: the point I want to make here is animal model are not predictive of all human being.

DR. SINGPURWALLA: Okay. So--

DR. YU: that's the key.

DR. SINGPURWALLA: Okay. So don't put r-square. Okay? Just put it that way.

And the top one doesn't make sense--the r-square of .71.

DR. YU: Uh-huh.

DR. SINGPURWALLA: It seems approximately linear to me--notwithstanding Marvin's comment. [Laughs.]

So the first one does make sense. The second one--I don't know how many--you show a lot of observations--

DR. YU: Yes, there's 18 points.

DR. SINGPURWALLA: No, the second one--the QSBR model.

DR. YU: Okay--yes, this is 18 points. Yes.

DR. SINGPURWALLA: I think you have more than 18.

DR. YU: 20.

DR. SINGPURWALLA: Okay--whatever it is. Again, r-square doesn't make sense there--does it?

DR. YU: Well, I guess--you know, I said, you know, when you look at r-square, .6 or .7, statistically probably is not meaningful at all. But, I guess, from physiological, pharmaceutical perspectives, that at least gives us some indications what could be potentially correlation coefficient; that whether it's good or bad.

I hope I answered your questions. [Laughs.]

DR. SINGPURWALLA: Yes. Fine.

CHAIRMAN KIBBE: Ken, you want to wrap this up?

DR. MORRIS: A general question, I guess, Lawrence--you know, the charge of looking at how we're adjusting the Critical Path or, how, you know, that the Critical Path Initiative is being addressed--given that a lot of what you're talking about isn't really generic drug-directed--sort of taking that as a given for the moment, if it's adding to the overall Critical Path, it's probably still valuable.

But if you look at the larger picture, and

you look at, like, your CAT slide, which turns out to be a popular slide--you don't have to put it up--but I guess the thing that jumps out--and maybe this is jumping forward to tomorrow a little bit, is that this all presupposes that the dosage form consistency is there to begin with when we're talking about the bioequivalence.

VOICE: [Off mike.]

CHAIRMAN KIBBE: Oh, you're mike's off.

DR. YU: You're absolutely correct. And this scenario, where I'm not looking--it's useful, these slides, we have not looked at how formulation impact. Impact, if you look at formulation impact for immediate-release dosage form, you have a suspension, different particle size. I can talk hours.

In terms of your first question, is this absolutely generic? Probably not. It's actually apply equall for drug discovery and development innovators. I guess my Director at the bureau is so nice he did not criticize, allow me to [INAUDIBLE] here. So that's--I have to say it

comes out sometimes in my research--not my mission to talk about some of the prediction bioavailability, bioequivalence.

DR. MORRIS: Yeah, I didn't really--

DR. YU: Well, same mission, which is to protect and advance public health. I'm sorry--go ahead.

DR. MORRIS: No, I didn't mean it as a criticism. I was just saying that--I'm just not sure that the immediate applicability of this is with the generics. But--

DR. YU: Yes, this is equally applied to innovators. I guess, no matter where I am, whether it's in the Office of Generic Drugs, or my previous position, Office of Testing and Research, our mission is to protect and advance public health. That's why--is part of the reason, I guess, why my director, so he's so nice, did not correct it.

CHAIRMAN KIBBE: Okay. I think we need to--

DR. HUSSAIN: Clarify one point, which I didn't--

CHAIRMAN KIBBE: I guess we don't need to go on.

[Laughter.]

DR. HUSSAIN: No, I think, in listening to the talk, the message that Lawrence was delivering with respect to dissolution for quality, and dissolution for predicting performance, just to further clarify what I think I thought process is, I think--for the last 20 years we have sort of merged the two together. And essentially what we're looking at is separating those out. There's a quality-control function, and there's a function for performance prediction. And those have to be addressed differently. That's the message that Lawrence was giving.

DR. YU: Thank you, yes. That made it very clear.

Thanks.

CHAIRMAN KIBBE: Thank you. Thank you, Lawrence.

Jurgen, you're not going to let us end

here, huh? All right.

DR. VENITZ: Is it on? Okay.

DR. YU: You have two minutes.

DR. VENITZ: I do? Okay.

DR. YU: [Laughs.]

DR. VENITZ: Okay, you have to count.

First, again, the same comment ethat I made earlier today--I obviously commend you for using quantitative methods to predict, as opposed to always requiring measure, measure.

DR. YU: Thank you.

DR. VENITZ: I do concur with the previous--with Ken's basically, statement that here you're talking about drug substances when you do your quantitative structure activity.

DR. YU: Yes.

DR. VENITZ: Given the fact that you are at OGD, I think you should also focus on excipients, and products; in other wordsthe , what is formulation effect? And I'm not sure whether you can have those nice models that you showed us, that are very meaningful to come up with NMEs and

figuring out what the chemical structure may be, related to bioavailability.

The second--so, excipient effect and food effect, to me, is something in terms of Critical Path that's important--not just predicting drug substances.

I do urge you to continue to work on the BCS, because I'm pretty sure in a couple of years you're going to come to this committee, or the next generation of committee members, for Class III, and you might make the same recommendation for Class III that you just, four years ago, made for Class I drugs.

DR. YU: Ajaz made, yeah.

DR. VENITZ: Or Ajaz made.

Two more comments: clinical bioequivalence--that's obviously something that this committee pointed around for quite some time. And you made the observation--which is a true observation--that clinical bioequivalence means you need a large number of patients, because you have lots of variability.

But I would take that argument around, and I'd say two things: number one, you're now testing the product in the intended population. So you have the benefit of getting away from healthy, usually male, volunteers, where you assess bioequivalence.

DR. YU: That's correct.

DR. VENITZ: Number two, what is the magic rule that requires you to have confidence in the value of 80 to 120, or 125--as we do for areas under the curve? Why can't you/clinicians define a minimum difference that is perfectly acceptable? We do that all the time for non-inferiority trials--in the clinical area. So why can't we use that to assess this concept of clinical or therapeutic bioavailability to get around this sample size that is going to go up exponentially?

The last comment--the question that you had on the dissolution testing, where you asked what is--is this just monitoring product performance, or is this something that is more meaningful? Well, the short answer is: it

depends. If you have an in vitro-in vivo correlation, it is not only something that you can monitor, but it's something that actually can be translated in in vivo performance.

So part of what you--maybe as part of your research--want to look at, under what circumstances do you have IV, IVC for simple dissolution test, at a single pH? And the complex GI tract--actually we'd use this to a beaker with solution in it?

Anyway--thank you.

DR. YU: Thank you. Do I have time for comment?

CHAIRMAN KIBBE: Thank you, Jurgen.

Yes, you have time for comment. We are planning, now, to extend the meeting this afternoon to 7:30 p.m., so--

[Laughter.]

DR. YU: [Laughs.] I guess the excipient effect I will show in my BCS slides, not show in bioavailability prediction slides.

In fact, the first publication, Molecular Pharmaceutics, 2004, is deal with food effect. So

where I just want to say that we're investigating effect of excipients on absorption, on bioavailability and bioequivalence.

And your--I guess I forgot your other comment, so I wouldn't have to comment on that. [Laughs.]

CHAIRMAN KIBBE: That's nice.

Let me just throw out that I agree with Jurgen's penultimate comment.

VOICE: [Off mike.] Figure out what that means.

[Laughter.]

CHAIRMAN KIBBE: We have an opportunity here to show a real sense of cooperation between academia, industry and the FDA.

We have a series of speakers, all of which are claiming they're going to use 30 minutes. Lawrence said he was going to take 20. It was 47.

[Laughter.]

If the other speakers are on the same track--mostly because we ask lots of questions--all really good ones--we will, indeed, be here 'til

7:30.

So, let's try to focus ourselves on the talks at hand, move through them quickly. And anybody who has more than 25 slides should be embarrassed.

[Laughter.]

All right?

We're going to start out with Dr. Rosenberg, on the Critical Path Initiatives--the Division of Therapeutic Proteins' perspective.

Office of Biotechnology Products--Current Research and Future Plans

DR. ROSENBERG: It's a pleasure to talk to you about our perspective on Critical Path.

So--I think it's important to start with why--how the Critical Path Initiative evolved. And it evolved, of course, because of the dramatic decrease in novel drug and biological product license applications.

[Slide.]

so what you can see here is that, from the mid-'90s there's been a steady overall decrease.

And more than, I think, just the decrease in numbers, we've really had a failure to develop therapeutics and vaccines to address difficult diseases. There's some diseases for which there hasn't been an improvement in therapy for over 30 years.

So, coupled with this general decrease in novel product development, there's really been, of course, a high candidate drug failure rate.

[Slide.]

And it's pretty dismal to look at these statistics. So, I mean, the last two--so a drug entering Phase 1 in the year 2000 is less likely to reach market than one entering Phase I in 1985. And more sobering I think, in fact, is the fact that about 50 percent of Phase III studies fail due to lack of efficacy.

So there's really a lot of uncertainty by the time many compounds are entering Phase III trials. And Bob Temple will go on about why that is, and how to improve that. But that's not the subject topic here.

[Slide.]

So this isn't--this sort of dismal picture isn't for lack of trying. What you can see in this slide is that, in fact, there's been an enormous amount of money and effort dumped into research and development, starting in the early '90s, and that it certainly outstrips, dramatically, the number of new chemical entity approvals.

[Slide.]

So there are many factors that contribute to this decline in new product applications. And certainly one that has been cited is the failure of novel methodologies and treatments to achieve practical application. So, you know, all of the wonderful technologies that have come up in the past 10 or 15 years--many of them have really not seen very much in the way of a practical application.

[Slide.]

And I think getting industry's sort of post mortem analysis on this is very important and interesting. So, a comment from Roche was that "I

think we got too enamored of technology and lost focus of what to do. The 1990s were really a boon for in terms of science, but we forgot that we needed to link all of that to disease."

And the second comment--from Adventis--"We though we would very quickly validate targets that were critical to disease and agonize or inhibit them as a way to start to find a drug...and what we found, in fact, is that validating targets takes a lot of time. And this is one of the big disappointments of this era."

So, I think, nowhere is this--I mean, it's key that we have a sort of naivete about product development. And I think this is what the Critical Path is trying to address--to take this naivete, to do some good science, and to perhaps shorten the length of time it takes from a great idea to commercialization.

[Slide.]

And I think nowhere is this better illustrated than in the development of a product that we regulate in the Office of Biotechnology

Products, and that is monoclonal antibody development.

And this timeline is a little bit warped, in the sense that it doesn't start at the beginning; because the beginning of this timeline is 1975, when Kohler and Millstein developed the hypodermic technology that would make it possible to produce monoclonals.

And so what you can see is there's about a 20-year lag period before you have a real flowering of products. And so I think that Critical Path asks a question, and that question is: can we shorten this time?

And it's--I don't think it's an assured thing, but I think it is certainly worth a valient effort.

[Slide.]

So let's focus a little bit more now on biotechnology products, and biological therapeutics, which is the group of products that our office regulates.

So, one of the reasons that there has been

a decrease in numbers of these products is that there has been a dramatic increase in the length of clinical development time. And you can see here, from the 1980s, through 2002, you know just this linear increase in development time. And that's coupled with, pretty much, preservation of the approval--the length of time it takes to approve these products.

[Slide.]

And that differs from the case of small molecular drugs, where in both the clinical phase and review times have diminished or pretty much leveled off since the early 1990s.

[Slide.]

So what is it about biological therapeutics that has caused such a length in development time? Well, for one, there's a really--a big shift in disease indications since the mid-1980s, late 1980s. More and more, chronic diseases are being assessed. And, of course, longer trials are necessary in the case of chronic diseases, to both the assess the efficacy of the

product, but as well as the durability of responses is key.

And even more important, I think, there's been a shift to therapeutic products whose mechanism of action and toxicities were less well understood. So, what was encountered in these clinical trials were unexpected and difficult toxicities, as well as a difficult in developing appropriate surrogate endpoints that would allow for shortening and greater efficiency of clinical trials.

[Slide.]

So how can FDA help? As I said, I think Critical Path is a great tool to try and address the enhancement in product development efficiency. But I think it's important to realize that FDA and industry still will have different roles.

According to this review, the ultimate goal, of course, of FDA and industry is the same: to provide patients with access to new, safe and effective treatments. And what's really at stress here is that coordination and cooperation are

required.

And the comment here is that FDA can only assist in the process. And I think Critical Path is trying to take this "only assist" into "assist greatly."

[Slide.]

In addition, we're not the only partners here--and this has been mentioned before. There are other players: disease-specific advocacy groups, NIH, CDC, etcetera. And the NIH recently has launched their "Road Map," which is very much targeted for drug development. And they have, you know, three basic initiatives within this Road Map. And so FDA is going to have to work, not only with industry, but also with NIH, as well as other advocacy groups in moving this--in enhancing the efficiency of product development.

[Slide.]

Now, this has also been mentioned--but FDA is uniquely positioned to identify and overcome challenges to product development. Reviewers can identify common themes and systematic weaknesses

across similar products, and that based on such knowledge, reviewers can formulate guidance documents and clearly offer industry sage advice about pitfalls.

Now, I think it's worth it to mention that guidance documetns have actually be shown to foster product development; that they improve the changes of an initial success of a marketing application, and they shorten time to approval. So there is research that verifies that, and so I think it's very critical to have scientific personnel that can promulgate very helpful guidances.

[Slide.]

So what are FDA strategies for speeding innovate therapies to market? The first one was actually in 2002, and it was called "Improving Innovation in Medical Technology: Beyond 2002." And this one particularly highlighted the importance of guidance documents in avoiding multi-cycle reviews.

And, of course now we have Critical Path.

[Slide.]

So the Critical Path, as we all have heard, it's a method to develop new tools, to imiprove predictions regarding safety and efficacy of new products in a faster time at lower cost.

And it essentially supports research--clinical and otherwise--for applied sciences needed for medical product development.

[Slide.]

You've all seen this. Critical path goes to some translational research, through to product launch. But actually, in our view, knowing the trouble that biological therapeutics can get into following marketing, and following licensure, we think it goes well beyond that, into post-licensure phases.

[Slide.]

Again, Critical Path involves issues of safety, efficacy and industrialization. And our scientists, in the Office of Biotechnology Products, are very expert in all of these aspects--or certainly in targted areas of all of these aspects of product development. And, as I

say, underestimated here is post-licensure issues.

[Slide.]

So, what sort of personnel does one need to negotiate this Critical Path? Well, for biological therapeutics we think that the researcher/reviewer is ideally positioned to advance the Critical Path. So a researcher/reviewer is a sort of hybrid species; this is a person who does a lot of regulation. This person is a producdt expert. They're absolutely integral to the regulatory process at all stages of product development, and they provide scientific expertise on multiple levels: product manufacture, including inspections--all of our reviewers go on inspections; product--this is an expert in product characterization, including mechanisms of action, in vivo bioactivity and toxicities. The researcher reviewer is also an expert in some analytical methods, and in some animal modeling. But the researcher/reviewer also has a key role in policy formulation and promulgating guidances.

[Slide.]

So the basis for the regulatory expertise of the researcher/reviewer is engagement in a high quality research program. So the researcher/reviewer is required to maintain an active laboratory reseaerch program in the field relevant to the review area. This person must publish findings in peer reviewed, high quality journals, and they must undergo site visit evaluations of their program every four years, and yearly internal evaluations. And, in fact, our promotions are promulgated more on our research expertise, and our research accomplishments almost than our regulatory accomplishments.

[Slide.]

So, interestingly, this requirement for a regulator who is intimately familiar with cutting-edge technology is very much in sync with findings that a subcommittee of the FDA Science Board made back in 1998, when they said, 'It is the consensus of the Committee that FDA requires a strong laboratory research focus and not a virtual

science review process; otherwise we risk the potential to damage not only the health of the population of the U.S., but also the health of our economy."

And I think the health of both are clearly in danger when we can't get new products out.

[Slide.]

So this group also went on to say that regulators and policy makers require expert knowledge and first-hand experience with the latest technology being applied to biological products; and that an intramural research porgram is required to assess risks of new therapies, to develop assays and new approaches to increase efficacy and safety, and reduce risks. It sounds a lot like Critical Path to me.

Moreover, I think a very strong point they made was that a strong, well maintained intramural research program provides the basis for a climate of science and scientific communication with FDA. They emphasized retaining high-quality scientific staff, but I think the permeation of science into

the review process is absolutely paramount.

[Slide.]

Okay, let's go on--just skip this.

[Slide.]

So let's go to my division--the Division of Therapeutic Proteins. This may be too small to read, but the only point I wanted to make is that all of our reviwers--and we do have some full-time reviewers--are spread among three laboratories: the Laboratory of Immunology, the Laboratory of Biochemistry, and the Laboratory of Chemistry. And we think that this is in keeping with keeping the culture of science permeated into the review process.

[Slide.]

Our division regulates an enormous diversity of products. We have 37 total licensed products; we have 30 novel molecular entities. We have many naturally-derived products--mostly recombinants, however; and really very minimal "me too" products. We have several interferons, for example.

We regulate many engineered versions of prototype products that are designed to enhance PK or other product characteristics; pegylated products. Many of our products have site-directed mutagenesis for hyperglycosylation, as well as other enhancements.

Our products are produced in very diverse cell substrates; from bacteria, yeast, insect cells, rodent cells, human, as well as transgenic animals and, soon to be, plants. And the manufacturing process is unique for each of our products.

[Slide.]

So the products that we regulate--I think you're familiar with: interferons, interleukins, thrombolytics, anti-thrombotics, therapeutic enzymes; all the ematolic growth factors, neurotrophic growth factors; chemokines--which are a novel area for us; wound healing products; toxin-fusion molecules; angiogenesis and anti-angiogenesis agents; immunomodulators, receptor antagonists, lectins; and, most

importantly, I left off cosmetics. We also have botox. We're very proud of that product.

[Slide.]

So what are the principal scientific issues--and regulatory challenges--for us?

We've got a lot of them in our division. Comparability is always a paramount issue, because there are no analytical techniques that will precisely define the 3-D structure of our complex proteins, we have to use a variety of techniques to establish comparabilitiy. And sometimes that actually requires animal studies and sometimes clinical trials. And we're engaged in a great exercise of this right now, in our follow-on biologicals initiative.

All proteins are potentially immunogenic, and so we have problems with immunogenicity. We have hypersensitivity responses, we have neutralizing antibody responses. And these can really blow up in product development.

Potency assessments--as I said, because no analytical technique--and one--is good at really

defining the 3-D structure, we use a potency assay, which is an activity assay which gives you a clue about product protein conformation. And that differs quite a bit, in some respects, from small molecule regulation.

Our products have been the subject of product counterfeit--on both Neupogen and Epogen. And so we're working th the Office of the Commissioner in formulating responses to that.

We've also faced novel transgenically produced products. We're going to get products produced in chicken eggs, as well as plants. And those raise very novel safety issues--and efficacy issues, as well.

And we're always faced with infectious disease transmission because of the way our products are produced, and the materials that are used to produce them.

[Slide.]

So, as product experts, we have a very keen knowledge of pitfalls in product development, from pre-clinical studies to Phase I and II

studies; immunogenicity, unexpected adverse events, lack of appropriate animal models. Certainly, mechanism of action, when it's not fully evaluated, can be very problematic.

[Slide.]

in Phase III, the development of validated potency assays are a real pitfuall in product development, as well as changing manufacturing in the middle of Phase III studies, which really wreaks havoc.

And so we really--you know, we spend a lot of time with sponsors trying to stear them away from these pitfalls. And I think you'll see that our style of communication is highly valued by industry, who feels that it's, in fact, vital for more efficient product development.

I'm just going to skip over some of the clinical ones.

[Slide.]

So, our Critical Path focus for our division is basically to support ongoing Critical Path projects. And we think of those as pertaining

to entry of products with novel mechanisms of action--and that would encompass research that investigates mechanisms of action of new products; research that establishes new animal models for assessment of safety and efficacy; and research that provides new or improved products to the piplines.

[Slide.]

Moreover, we recognize very well the barriers and hurdles to product development, including immunogenicity and potency assessment. And so we value research that overcomes these barriers to product development; moreover, activities to standardize assays--this is very important when you're trying to compare across different products.

Moreover, the last type of research we think is highly critical-path appropriate is identification of surrogate endpoints and biomarkers for safety and efficacy. And so we really value research that identifies novel biomarkers, as well as activities to gain consensus

on appropriate surrogate markers.

[Slide.]

So, some of the programs that we have really very much addressed directly with Critical Path issues: one of them is the development of CpG oligonucleotides as immunomodulators for infectious diseases. Daniela Verthelyi is the principal investigator, and so she investigates CpG oligonucleotides as they interact with toll like receptor, as well as other potential toll like receptor ligands. And she studies primates; she's interested in identification of surrogate markers of immune protection, and development of novel TLR agonists. This project also has high relevance to bioterrorist situations; can we enhance the immune response by fiddling with these toll like receptors to bioterrorist agents?

[Slide.]

The second project that directly addresses Critical Path issues is a research project that's focused on chemokines, which are chemo-attractant cytokines. And we're ver increasingly coming to

appreciate the fact that these products are absolutely critical for cell migration in the seetings of inflammation, metastasis, angiogenesis, and atherosclerosis. Mike Norcross is the principal investigator. And, within his research, he is developing methods to assess the potency of these products. Potency, as you can imagine, is very difficult to assess for a product that's a chemo-attractant product. Those are very squishy assays; very variable. So, this has been a real problem in product development.

He is, as well, trying to evaluate and develop methods for non-clinical screening of anti-viral biological products, as well as the development and validation of biomarkesr and surrogate endpoints for immune-based therapies for HIV infection.

[Slide.]

And just to show you a little bit of a schematic here--so you have bacterial products, such as LPS, or CpG oligos that tickle toll like receptors that are present on macrophages and

dendritic cells--antigen-presenting cells--that cause them to emit chemokines, such as IL8, MIP1-alpha, IP10, and these cause chemoattraction of various immune mediators, as well as cause trafficking of tumor cells to distant cites.

So it's a very exciting area, and I think having such expertise is critical to the product development.

[Slide.]

Dr. Donnelly also has a program which we think fits directly into Critical Path. He is focusing on signaling pathways of novel interleukins and inferons; specifically, he's defining signal transduction pathways for new cytokines, new interleukins, ILs 19, 20 and 22, as well as defining biological properties of a new interferon, which may be significantly less toxic than interferon-alpha. It's called interferon-lambda.

[Slide.]

Dr. Beaucage--who many of you may know--world-class chemist--basically has a program

to enhance the specificity and sensitivity of oligonucleotide microarrays which, of course, are used for myriad purposes. And so he has focused on detection and quantification of bacterial and viral nucleic acid contaminants in biologicals, including blood products. This methodology would be helpful for high-throughput screening of point mutations, or single-nucleotide polymorphisms that might dispose to human disease. And, of course, these are used widely as gene expression assays to evaluate potentially the safety and efficacy of drugs.

[Slide.]

So, those are the projects we think are directly relevant to Critical Path.

Others, I think, we conceive of as being supportive of Critical Path; perhaps not as highly targeted, but nevertheless, absolutely vital to product development.

So, Dr. Shacter's program, and Dr. Johnson's program are focused on novel anti-cancer treatments. With Dr. Shacter, modulation of signal

transduction pathways to enhance tumor cell dealth in response to chemotherapeutic agency, and the investigation of antioxidants as potential chemoprotective agents to limit side effects from cehmotherapy. And Dr. Johnson is focused on enzymology of epidermal growth factor receptor signaling, as well as identification of novel signaling molecules.

[Slide.]

Many of our programs are immunologically oriented. And as I said, immunogenicity is a critical issue along the Critical Path.

So, all of our proteins are potentially immogenic. As I said, we can get hypersensitivity, anaphylactic-type responses, or IgG antibodies that will neutralize a therapeutic protein, or block the action of an endogenous homolog of that therapeutic. And immunogenicity has killed products in development; certlain from epoeitin, CNTF, GM-CSF-IL-3 fusion molecules, as well, it limits the efficacy for many giological therapeutics, such as therapeutic enzymes, interferons alpha and beta,

and asparaginase.

And it poes an ongoing concern for licensed products followoing changes in manufacture, packaging and clinical indication. And I think most of you are aware of the situation with Epo and the induction of pre-red cell eplasia, due to changes in the packaging of Epresx.

AS well, there's a lack of standardized assays for comparison across products in the same class. And this is a problem.

[Slide.]

So I think, you know, for immunogenicity most of us conceive of it as being capable of doing the following, which is to block the development. Actually, interesting--it was supposed to blow up. So my Papa Haydn slide didn't work very well.

[Slide.]

So, the immunogenicity concerns and the projects that address this have to do with understanding the mechanism by which antibody responses to proteins are switched to cause anaphylaxis. And this also will have, I think,

some meaning for small molecular drug development, because they are not without their hypersensitivity response; research to develop better animal models to assess immune tolerance and autoimmunity; research to dissect immune responses to embryonic stem cells; and we are also participating in international efforts to standardize antibody assays for erythropoietin products.

[Slide.]

Some new Critical Path projects that we foresee, looking into the future: nanotechnology is being highly toutedfor potential abilities to deliver productsi n novel ways. This may also actually present big problems immunogenicity for vaccines that many of these approaches might be terrific in enhancing immunogenicity, but they could be devastating for therapeutic protein products. And we think this is worth investigating so that this technology--at least for biological therapeutics is not stopped prematurely.

For therapeutic enzymes, the immune response does limit efficacy, particularly of

life-saving products for patients who lack some endogenous enzymes which are critical for life. And so we think that tolerance induction should be explored in that setting.

Protein aggregates are a perpetual problem that induce immunogenicity. However, the specifications for aggregates are essentially set on manufacturing experience, not on risk. And so we think it would be critical to evaluate the risk of protein aggregates. What level of aggregates? What kinds of aggregates? And how are they delivered? What is responsible and what is important in incurring risk?

And also the development of buidance documents we think would be a very valid Critical Path project.

[Slide.]

As well, some of our research--out of some of our research has come an idea for a novel product which would promote treatment of sepsis, which is a disease that is notoriously refractory to treatment. And Dr. Shacter's lab has identified

protein S as being critical for many functions, among which are clearance of apoptotic cells. But since activated protein C works in conjunction with activated protein--with proten S, we think that our research suggests that addition of protein S to the treatment protocol that uses activated protein C will improve efficacy. And so we would like to develop that as a therapeutic protein. Of course we would like to get that to a commercial entity that would develop it.

[Slide.]

I'm coming to a close now. But we also think that communication is a critical component of Critical Path. And an industry survey done last year that looked at good review management practices, found that the kidns of communications we had--and that were alluded to, I believe, in an earlier talk--that is open, honest communication; informal communiations; regular status updates; timely communication of issues as they arise; and clear and concise FDA responses with explanation of positions--these were all review practices while we

were in CBER, and we have carried over to CDER, and we certainly hope that, given that communication is vital, that these will be carried on.

[Slide.]

And so I will skip through this. You can read through it yourselves.

[Slide.]

Other DTP Critical Path activities involve participation in ICH proceedings; and particularly with regard to to comparability guidance. So Dr. Cherney, who is the Deputy Division Director is the lead on the ICH !5e, and so, again, the importance of guidance documents can't be overemphasized, in terms of enhancing product development efficiency.

Another one of our personnel, Dr. Kirschner, is involved in standardization of antibody assays for erythropoietin products, which is an international effort. And, moreover, the suport of risk-based approaches to GMP and inspectional issues is something that we also think is a vital Critical Path activity. We need to switch from checklist approaches to GMP, to

risk-based approaches. And we're strongly participating in that.

[Slide.]

So, in summary, DTP strongly supports Critical Path efforts to facilitate development of new products. We think that we have some projects that are doing that now, and should be better supported. We have identified new projects that we think should be funded to enhance this process.

Other activities, including the development of guidance, adoption of a risk-based approach to GMPs, and maintenance of communication form at with industry we also think are vital.

So--I'll end with that. And I hope I didn't go too much over time.

CHAIRMAN KIBBE: Thank you very much. Outstanding! All right.

You actually have allowed us five minutes worth of question time. And we'll let Meryl have it all.

DR. KAROL: Okay, thank you. That's a very impressive summary of what you're doing.

I wondered if you're placing emphasis on development eof biomarkers for not only immunogenicity, but hypersensitivity, tolerance as well? You know, could you tell us about those efforts, to develop biomarkers to predict these effects?

DR. ROSENBERG: Yes, I think--you know, we do a lot of animal modeling. And so most of our programs have to do with rodent models, and looking at tolerance, and looking at immunogenicity, particularly--Dr. Verthelyi's program.

Now, she has taken this one step higher, to primate models, in trying to come up with surrogate markers. And, you know, I think this is something that we're putting an emphasis on. I don't know that we have a real formal look at that at this point, or we can really report on that. But that is something that we would like to emphasize better.

CHAIRMAN KIBBE: Ken? You really--

DR. MORRIS: I really have a question. I really have one.

CHAIRMAN KIBBE: well, go ahead.

DR. MORRIS: But it's not as technical, I don't think.

Given the Tufts projections, as well as the statistics you showed on success, have you attempted to factor the contribution of the various thrusts that you're pursuing to determine--in terms of prioritization?

DR. ROSENBERG: So--in terms of--yes. I mean, I think that what we're trying to emphasize are aspects that have been proven to do something. So, certainly, communication is a critical aspect, and development of guidance is--has been shown--

DR. MORRIS: Yes, actually, I guess I was thinking more about your research thrust, but--

DR. ROSENBERG: Yes--so those are emphasized.

The research thrusts--yes, I think that what--you know, what we're looking at here is the research projects that we have that absolutely address Critical Path issues we would like to expand. Of course, resources are limited, and

there's just a certain amount we can do. But the one's we've identified I think are absolutely critical for these novel emerging technologies. And, as we've seen, you know, people can be very naive about what one can expect from those.

So looking--you know, having looked at that, and looking at what's coming ahead, we would like to investigate, you know, the immunogenicity concerns for nanotechnology. We would like to look--you know--we would like to be able to look at that. I can't do that with the personnel limitations I have now. We would need funding and personnel to do that.

So--as well as, you know, bioterrorism is a very important factor now, and we think we have the ability to address a treatment for that, which would be the CpG oligonucleotides, or some similar pathogen-associated molecular pattern ligand.

So those, I think--we have good models, and we would like to push forward on those in particular.

DR. MORRIS: Thank you.

CHAIRMAN KIBBE: Melvin, you want to--

DR. KOCH: Yes, just--excellent presentation. I was just wondering, in many of the needs you expressed--and they sound like ideal candidates for CRADAs. And has that been explored at all?

DR. ROSENBERG: Yes. We certainly try to develop those where we can. It's a little tough, given some constraints. Because, of course, as soon as you develop a CRADA, you know, you're limited in what you can participate with, in terms of regulatory action. So, you know, you're always sort of caught between a rock and a hard place. But--yes, we are trying to develop CRADAs--for some of those projects--and have been successful. Dr. Beaucage has been successful, particularly, with the micro-arrays over the years, and getting CRADAs.

CHAIRMAN KIBBE: Thank you very much.

DR. KAROL: One more question? How are we from developing SAR models for protein allogenicity? Is that at all on the horizon?

DR. ROSENBERG: Whoa! That's a very good question. And I don't know the answer to that. I really can't tell you. I think I would have to talk to somebody who's more of--more focused on allergy.

CHAIRMAN KIBBE: Thank you very much.

DR. ROSENBERG: Thank you.

CHAIRMAN KIBBE: Next, we have Steve Koslowski. Sever has 64 slides--

[Laughter.]

DR. KOZLOWSKI: Oh, I'm already in trouble.

CHAIRMAN KIBBE: You're under the gun, Steve.

DR. KOZLOWSKI: Well, thank you for having me speak. And I will try and move quickly.

[Slide.]

So I'm going to talk about the Division of Monoclonal Antibodies, which is the other biotechnology product division. I'm going to talk a little bit about quality, and I'm going to kind of take the lead from one of Ajaz's slides, and

talk about connecting the dots; then about a concept called biological characterization; the reserch reviewer model, which we can go through quickly, because Amy already covered that; the organization of our division--our products; ongoing research' Critical Path; and then sort of summarizing Critical Pathways and directions.

So I want to put up a slide that Ajaz gave me, about a way of looking at integrated quality.

[Slide.]

The fact that different disciplines in review from clinical to manufacturing TO CGMPs to PAT all need to be interconnected in a useful way. And I'd like to take a little bit of a slice of that figure--

[Slide.]

--and actually take a way a lot of points, and basically leave the CMC relationship to clinical attributes, and talk aout connecting one dot to begin with: the chemistry of a product--or, basically, its complete structure, to those things that we control in evaluating it.

So, clearly, the characterization of a product leads to what we eventually use as classical specifications-0-or at least how we've talked about productsi n the past.

[Slide.]

And there are ICH guidelines on this. You need to characterize a biotech product in order to pick the relevant specifications that you use for quality control. You choose these specifications to confirm quality--and obvious, you don't recharacterize the product each time. But what's critical is those molecular and biological characteristics that are necessary for connecting to safety and efficacy.

[Slide.]

And I think those are really the weakest links, because the connections between what structure really matters for clinical outcome--what attributes are important--and what controls in manufacturing, or what controls in regular testing, confirming these things is a very hard link to make.

And clearly you need to know these relevant structural attributes to take advantage of this CGMP, or more global way of looking at things. So, again, what processes you need to control; what structural attributes are important.

[Slide.]

That leads me to what I'll call biological characterization.

So I'll start with talking about our molecules. Amy certainly referred to the fact that the biotech proteins--or products--tend to be very large. And this is an example of a third of a monoclonal antibody--an Fab section compared to a statin.

[Slide.]

And so, clearly, the large molecule has issues, not only of primary sequence, but higher order structure, post-translational modifications, and it is a very heterogeneous protein. In fact, the variability in proteins--in fact in the desired product--are greater in size than the size of a statin.

And, again, comparing molecular weight: 150,000 to 400.

[Slide.]

So this leads to a problem--as Amy pointed to--for complex molecules--as again, in the ICH guidance--physiochemical information at least presently insufficient to define higher order structure.

[Slide.]

And so what we use--and it's an imperfect thing--but we use biological activity as the surrogate, sosrt of, for full biochemical characterization.

And so biological actiivty is specific capacity of a product to achieve a particular effect. And potency is the way we measure that. We use a variety of bioassays: animal based, cell culture based, biochemical--sometimes receptor ligand binding.

[Slide.]

There's a whole continuum of these assays, which go from very simple assays to ones that are

very complex. The complex assays--like, ideally, a clinical study--is true potency, but its reproducibility and its utility as an assay is very poor. On the other hand, simple assays are very useful from a validation perspective, but may not really reflect what you want to look for.

[Slide.]

So how do we choose the relevant biologic activity as a surrogate for structure? So assessment of bioological properties is an essential step in the characterization. And so, by characterizing the biological responses that are generated by the product, one should be able to pick a good assay.

[Slide.]

So just like you characterize the structure to pick the physiochemical attributes, you need to characterize the biological effects to pick a potency assay, and to define those characters that ensure safety and efficacy. And, again, defning those characteristics--what attributes really matter--are crucial to the ideas

of risk management, CGMPs for the 21st century, and PAT. Because if you don't know what to control, you can't control it.

And that makes it also relevant to small molecules and achieving this ideal state where everything is connected, and you can avoid a lot of testing at the end, and you can truly know your process.

So I want to touch on two quick things: molecular mechanism of action, and biological plausibility.

[Slide.]

Molecular mechanism of action is--again, you need it for potency assays for therapeutic proteins. But for all CDER products, it will help you pick relevant physiochemical properties; sometimes predict toxicity, drug interactions and efficacy; and can be useful in choosing animal models and clinical monitoring early on, when you don't have enough data to really know what a protein or product is going to do.

[Slide.]

biological plausibility--we talked about biomarker development and validation. You need to be able to interpret early pharmacogenomic and proteomic data. When you have a large enough study, statistical data may be good enough. But when early on you need to make a decision that involves product development, biological plausibility is a critical part of assessing a biomarker. And one of the only ways to do that is to really understand the mechanistic issues, and to say that this marker or this gene makes sense.

[Slide.]

So if biological characterization is so critical to these issues, why is there such little guidance on how to do it?

If you look at the guidance of end-of-Phase 2 meetings, it talks about having "adequacy in physiochemical and biological characterization." The term is used. However, if you look in the parentheses: "peptide map," "structure," glycosylation"--no mention of what biological characterization is.

Later on, it talks about "bioassays," and metnions using a variety of materials in the bioactivity assay, not just the product itself--which is the beginning of biological characterization.

[Slide.]

What you would ideally want--and, again, this is difficult to do, and we're not saying that this can be done or should be done--but binding of the product; singal transduction pathways; cell culture effects; tissue studies; and in vivo studies--and sometimes multiple studies, because the same protein or same product can have multiple active sites.

To do this, you need relevant models. That means you need the right receptor, the right pathway, the right cells, tissues and species. To pick those, you need to know the molecular mechanism of action. However, if that's how you're defining it, you have a circular problem. It really is difficult to do this. There's no linear algorithm to really biologically characterizing

something. And so, again--I'll use another term from Ajaz--you really needs a systems approach. You need a way of dealing with this information to allow you to get the attributes that can allow you regulatory relief from controlling them.

And there's also product specificity. There's a lot more variability in a lot of these biological assays. And it's very expensive.

[Slide.]

So one approach--and we have companies who've actually done this--is to sort of have a matrix. So for--and I'll talk about using one or so lots, and using many lots for some of these things.

So in initial development--the lots very early on--you might look at multiple in vitro assays, and really get a good feel for what your developmental lots do; move on to testing some of those in more complex animal assays--transgenic models, sophisticated models that really try and target the relevant attributes. And then, again, in the end, when you have a validated bioassay, it

would be good to go back and look at all the lots.

Stressed lots--similar testing plan--because this is likely to start giving you variants that you can define as important or unimportant.

And then for some of those variants you might purify them, and then repeat some of othis testing.

In clinical lot manufacture, you're always going to have some lots that are at the extremes of the ranges. And use of those lots in some of these assays can also help you define this.

Ad, finally, the clinical lots, you know, should be looked at in the validated bioassay and sosmetimes in some of these other assays.

So having a sort of matrix approach to what you're looking at may help define the information that you need to help you avoid retesting and looking at all these attributes.

[Slide.]

To do this, there needs to be biology expertise. A biological characterization is only

as good as the data that supports it. Regulatory decisions are impacted by this sort of characterization. There needs to be a framework for interpreting this data, interpreting the assays, and defining what's needed.

And this expertise is going to become more important over time; in fact, it may be useful to actually have a guidance for how to approach biological characterization for some of these materials, and a mechanism for consulting people with the right expertise in order to do this.

And with the recent consolidation, CDER has now got some additional expertise in cell and molecular biology, which could play a role in somse of this.

[Slide.]

And, now, we talked about the research reviewer model--basically, research reviewers do both jobs. It's challenging. We're judged on productivity. We have to go through site visits and tenure committees, and we have the difficulty of multiple workloads.

On the other hand, the research reviewer model can serve as a form of catalysis and synergy, because basically we know not all reviewers can have active research program. It's economically unfeasible, and it doesn't make sense.

[Slide.]

But if you have a small nucleus of research reviewers, they can help encourage some issues in biochemical and biological characterization, process understanding, and mechanism. And they can consult on key decisions, and they can also network to NIH and other acadmic groups, OTR staff, and the full time review staff.

[Slide.]

Research is organized in funny ways. So, if you take disciplines like immunology, tumor biology, neuroscience and developmental biology, there may be people who have expertise in cytokines, or cell hormones related to this; adhesion related to these cells; and differentiation or in signal transduction. And there's a kind of a matrix. And you really can't

cover everything. But if you have a number of researchers--as Amy talked about in her division, and we have in our division--who cover a lot of these areas and things, you can often find points of intersection. And those points may involve research related to your question; NIH journal clubs that people participate in; academic conferences; and, finally, the literature itself--but this variety of networking that gives you access to information.

[Slide.]

So, briefly, about our organization. So we have three divisions: Molecular Development and Immunology--Margie Shapiro's the lab chief; the laboratory of Cell Biology--Kathleen Clouse is the lab chief; and the laboratory of Immunobiology--and I'm the lab chief. And each of these have three principal investigators. They look at lymphocyte and monocyte biology; tumor suppressors and oncogenes; cell-cell and cytokine-receptor interactions; signal transduction; and antibody interactions--which are very relevant to our

products; and manufacturing process validation.

[Slide.]

And our products--if you look at them in terms of indication--they tend to be either immunology or inflammatory-related or oncology-related. And therefore having expertise in immunology and tumor biollogy is very relvant to our products.

We have a number of approved products that relate to immunology or inflammation; some of them that share targets. We have to CD25s; we have a variety of isotypes--different species of antibodies, and anti-infective antibody products against cancer--again, some of them share targets like CD20.

[Slide.]

Our reviewers participate in inspections. We have imaging agents that are radio-labeled, and we're involved in developing guidance documents--points to consider for monoclonal antibody; plant transgenic products; orphan drug status-monoclonal antibodies. And we're also

involved in Q5e, although Barry's the lead on that. And we're involved in follow-on proteins.

[Slide.]

So, we have a research program. And this I'm going to have to go through extremely quickly.

So, we have groups that have studied particular chemistry. What I'd like to focus on is antibody structure.

[Slide.]

This is a schematic, based on crystal structure diagrams of an IgG molecure. The V region on top, with the DRs are the variable region, with a binding site which is a part of the antibody that leads to finding its target.

There are variety of other regions in the molecule which bind effector molecules like Fc receptors, complemin, and a variety of other receptors that mediate effector function. So the antibodies have lots of different active sites. They may be relevant for some things and not. They're also glycosylated, some versions a lot. IgG1 tends not to be as much, but this is also

relevant, in some cases, to PK and to effector functions.

[Slide.]

So we have Margie Shapiro's lab that looks at some of the things that generate antibody diversity. There are new technologies in making antibodies, like phase display, transgenic animals that express human antibody genes. They may lead to different binding sites--different diversity. They're not.

[Slide.]

And if you look at immunogenicity of antibodies--murine bio-similar, of which this looks at 8--more than half of the patients who get them develop antibodies against them no matter what. They're highly immunogenic.

If you take away the Fc region, and just have the top half binding site of the antibody, that immunogenicity goes down. If you make the Fc region human, and you leave the variable regions mouse, you find that the immunogenicity also is between 1 and 13 percent. Again, as Amy said, it's

almost impossible to judge these comparatively. So you have to take this with a grain of salt, because the assays vary.

But if you humanize the antibody--you make all of it human except for the binding site area, and some other amino acids, the immunogenicity also is low--maybe a bit lower. If you take a fully human antibody, which is one example of bi-phage display, it actually doesn't have a lower immunogenicity.

So the question really is: is the technology of making these antibodies relevant to how immunogenic they are. And she--and her lab is studying this.

[Slide.]

Antibodies have effoctor interactions. Complement recptors play a role. There's a new family of Fc receptors--it was found through the genome--which isn't known how it functions. And we have Dr. Mate Tolnay, a new investigator, who's going to look at whether or not those Fc receptors play a role in antibody function.

And Dr. Gerry Feldman has looked at immune complexes and how they signal responsiveness to cytokines. Again, that may play a role in how antibodies work.

[Slide.]

Now, in terms of the biological characterization--I think I'm going to try and just skip this. We have a lot of different projects related to lymphocyte signaling, on HIV, sustaining in reservoir; the EGF receptor--and all these projects relate to products that we have.

So if you look at adhesion costimulation molecules, we have a licensed antibody AGAINST LFA-1. And that information is useful on how its potency assay was looked at.

[Slide.]

We have antibodies herceptin against tumors which signal through a molecule called Cbl, and we have someone who works on that.

[Slide.]

And, again, I want to talk briefly about Wendy Weinberg's project. She looks as skin as a

model of differentiation, and is interested in p53--but not classic p52, but new members of this. So here's an example of cells growing under low calcium, and these cells have not differentiated. If you increase the calcium concentration, they differentiate; you see there's no more contact; they're much less likely to grow; and there's a decrease in the amount of proliferation. The S phase is down by 43 percent.

But if you add a variant of a p63 gene, which is a p53 family member, that no longer happens. They continue to grow, despite the fact that you're induced differentiation.

And the question about what these family of genes do in cancers is relevant. And I'm going to talk about that in a moment.

[Slide.]

We also have research regarding controls and manufacturing process--and relating to contaminants and process understanding.

[Slide.]

So the slide here is--you know, "This is a

brain; this is a brain on prions." You can see the spongioform degradation. And this is an image of how the prion protein is changed in conformation in order to cause disease.

But it turns out peptide's a prion signal, and they signal through the NF-kB pathway, and they signal through inducing cytokines. And they have different effects on different cell types.

And so information on this is useful in designing, potentially in the future, cell-based assays for prions--although they're not nearly sensitive enough to do that now--and potentially looking at the mechanism of the disease of this common contaminant.

[Slide.]

Kurt Brorson, who works with Kathleen Clouse's group, has made studies on retroviral testing, using Q-PCR-based assays, which are much easier and faster turnaround town; process understanding, in terms of the unit operations, the purification, chromatography.

[Slide.]

And here's an example of a bioreactor used to produce many of our products. The question is: what things can impact retrovirus expression? And his work has shown scale and nutrients don't seem to matter, but inducing agents and temperature do. And, again, butyrate increases the expression of retrovirus and increasing temperature does.

[Slide.]

Critical path--so, again, three dimensions--we've all seen that.

[Slide.]

In terms of Critical Path projects that should be defined as Critical Path--so you really need to define a problem, state the dimensions, and point out why the FDA--if the FDA's going to do this research--is in a unique position to do so; and what benefits go to what industry segments, and the role we can play, and the impact of the solution.

[Slide.]

So I'm going to go through this really quickly, because there are a number of

investigators who I think have very clear Critical Pathways. And one of them is the fact that anthrax toxin is potentially a target for treating and prophylaxis of anthrax, which is clearly a problem we're all familiar with. But the bioassays for anthrax toxin tend to be murine cell lines. And they die. And, in fact, human cell lines do not die from anthrax toxin. So is this r eally the right model to be looking at the efficacy of things that block anthrax toxin?

[Slide.]

And obviously this has medical utility and industrialization issues, and also counterbioterrorism. And the unique position of the FDA is, is we're the only group that sees all the INDs for anthrax therapeutics. And there's another unique aspect here is the FDA also plays a role in talking to the groups--like the CDC--that are involved in BioShield. So the FDA's in a sort of a funny role, because it's not only a regulator, it's in some ways a stakeholder, since the government is, you know, buying these things to

stockpile at some point in the future.

And, again, so David Fruct, who's doing this, has shown anthrax lethal toxin activates a particular pro-inflammatory cascade involving cytokines. There's been a huge debate in the literature of the role of cytokines. And I think he's provided strong evidence that they do matter.

And he's also been able to show some effects on human cells using this and, in fact, an enzyme that drives this.

[Slide.]

And I have a quick schematic. So anthrax toxin is composed of three components: the first one, PA needs to bind a receptor. It forms a hexomer. It then translocates the other toxin units into the cell--this one, lethal factor, effects MAP kinases, which are important to signal transduction. And these lead to cell death.

But David Fruct's lab has also shown they lead to IL-1b and IL-18 release. How this relates to pathogenesis is unclear. But it already represents a potential marker you could have for an

assay, for blocking the effect.

And he's also done some studies showing some effects in human cells--which, again, might make a more relevant bioassay.

[Slide.]

Wendy Weinberg--I showed you briefly her slide, about looking at p53-like products. And I think there is a huge lacking, in terms of goo preclinical models to predict treatments for cancer. have at least a number of products in which Phase III studies were done for the wrong indication, and later worked when the indication was shifted.

So, clearly, the preclinical models used to choose that first Phase iII study were in error. And making models where you have mice, where you have p53 knockouts, p63 knockouts--a variety of mice in which you can mimic how human cancers develop based on what genes are knocked out in them might make a much more powerful way of picking that first indication.

[Slide.]

And, again, Kurt Brorson, who looks at process-related things--and I'm just going to skip to a picture--

[Slide.]

--so a lot of our process uses a viral removal steps, including nanofiltration. So we filter away viruses. So how you test, and how you validate these filters is tricky. You certainly don't want to test the filter with a virus, if you can avoid it. It's more difficult to do, and you'd need containment procedures. And it's cumbersome. But you wouldn't like to depend entirely on things like gold particles, or a very poor surrogate for, really, the ability of the filter to remove viruses.

So Dr. Brorson's involved in using a phase--a bacteria phase--which is easy to grow, in testing these filters--and a good mimic for large viruses. And so the phase he uses is PR772, has been purified here by cesium chloride gradient, so you don't get clumps. Clumps are very misleading, because they look like they're cleared when, in

fact, your filter really can't filter out viruses of the right size. And, again, this is showing the purity by cesium chloride preps.

So, again, this has the potential to make a better way of testing these filters and showing that they really do the job they do.

[Slide.]

And there are a number of other industrialization-related projects, in terms of using gene arrays to look at cell culture changes. We're also interested in databases of some of our manufacturing experience. We sort of wanted a comparability database for a long time, but it's been a little slow to go.

[Slide.]

So to sort of summarize, in terms of Critical Pathways, historically, cell and molecular biology have always sat with basic research. But I think now they have evolved so they are involved in looking at clinical outcomes, in terms of pharmacogenomics, and proteomics, and they're involved in industrialization, because they offer

more sophisticated ways of measuring industrial processes. And they're clearly important in choosing the right pre-clinical development, the right potency assay, and quality issues.

[Slide.]

And, again, by defining the biology of a system better, you can pick the relevant physiochemical properties--and that's critical for cGMP and PAT--certainly, for our complex proteins. There's a potential for this to affect toxicity, drug interactions and efficacy, and even pick early-in-development models. We've had cases where, based on a biological effect that we would predict from basic science about a protein, we've talked to the clinical reviewers and we've said, "Well, maybe this should be an exclusion criteria." Or, "Maybe you should think about looking at this."

So this information really is relevant at all stages of development--and, again, plays a critical role in process validation and regulatory, fewer failed studies.

[Slide.]

So, I think a critical direction is really to better define "biological characterization." Clearly, we're not asking industry to test every lot of everything they've ever made, in every animal model you can think of. But the point is, by having good characterization of the mechanism of action, using a variety of models, sthat really leads into the fact that you can say "this parameter," "this glycoform" doesn't matter, and therefore avoid problems when you have comparability issues--you know, in terms of a difference there, and reduce, potentially, in the future, the actual specifications you have.

Again, ideally, we'd want a guidacne on thsi. It's--again, because it's non-linear it's ckind of ocmplicated to think about how to do this. And this plays a critical role for follow-on proteins. The better you can characterize the mechanism of action, the more confidence you are that a follow-on protein is going to do what you think it's going to do.

Again, we'd like to maintain this

biological expertise. We'd like to have research, you know, across the relevant areas for out products--which I'm calling "Critical Pathways," because it doesn't necessary fit the A, B, C, D, E, F of Critical Path.

We'd like to facilitate access to OBP biologists; interactions with other offices, with pharmacology and clinical review groups. We actually briefly had a conversation yesterday, in terms of the pharmacogenomic review process, could we play a role, in terms of helping define mechanistic questions about correlating markers? Again, Biotech Rounds with OBP and other clinical groups; and mechanism of action journal clubs, potentially, to talk about this; bioprocessing journal clubs--and, again, eventually mechanisms for consults on these issues.

[Slide.]

So--we also want to extend OBP into Critical Path projects, like some of the ones I've mentioned.

We talked about computers and

e-regulation. And I think relational databases are a verty useful thing. We have, in our division, a database Kurt Brorson is setting up for viral clearance; a database that Patrick Swann, our acting Deputy Director, has for review management, USAN names and targets; one for specifications; one for the risk of TSE. We have databases now we're trying to capture internal meeting summaries; workload databases; and, ideally, for monoclonal antibodies, wehre there's tremendous similarity between them, structural sequence information that we could compare between our products, and link to adverse events, would be very useful.

So, it seems all these databases--some of the Excel spreadsheets, and some of them more sophisticated--if we got somebody to make them a relational database, where you could work all the way through, that would be a very powerful tool, and potentially aid in the Critical Path.

And, again, our ultimate goal would be to use biological information, our research and our regulatory review, to enhance safety and facilitate

regulatory relief.

Thank you.

CHAIRMAN KIBBE: Impressive.

Questions?

[Pause.]

Either we were all so impressed, or we all need a break.

DR. KOCH: Well, I have a quick question.

If I understood correctly, where you have the industrialization intersecting with the Critical Pathway, you're inferring that's something like surface plasma and resonance, or something else that will actually be an interrogation of the process?

DR. KOZLOWSKI: Well, again, I think--for instance, surface plasma and resonance, for instance, you can sort of do--I guess not in a line, but you could look at binding off a process--

DR. KOCH: Right.

DR. KOZLOWSKI: --by filtering your two to a bio-core chip.

Yes--I think that would certainly--that

would be very PAT-like, to actually look at--

DR. KOCH: Right--that's what I was--

DR. KOZLOWSKI: --the binding of something on a biacore--say, straight out of a fermentor--

DR. KOCH: Right.

DR. KOZLOWSKI: --and look at what your conditions do.

DR. KOCH: Right. It becomes an analytical or monitoring tool.

DR. KOZLOWSKI: Right.

CHAIRMAN KIBBE: Anybody else?

[No response.]

Okay. Thank you very much.

I would liek to propose a short break--10 minutes. And then we'll get started with Jerry Collins at 3:13.

[Off the record.]

CHAIRMAN KIBBE: We need to get started. And I see by our colleague at the podium, who is now changing the entire proces, that we are almost ready.

What's wrong?

DR. COLLINS: The cursor was stuck, but it's back on now.

CHAIRMAN KIBBE: The cursor was stuck. There's nothing like having a stuck cursor to kind of ruin your afternoon.

[Pause.]

All right--Jerry Collins is going to talk to us about Critical Path initiatives in lab-based bioresearch of small molecules -my favorite kind of molecules, because I can draw the structures.

DR. COLLINS: There will be a structure quiz at the end, then.

Office of Testing and Research--Current Research and Future Plans

[Slide.]

DR. COLLINS: If you haven't gotten tired of trying to find something different in this diagram each time, my only point here is to emphasize that there are some areas of overlap between what NIH does in translational research, and what we consider Critical Path Initiative at

FDA; areas of overlap and areas of difference.

[Slide.]

We think about research--at least within the Office of Testing and Research--along the same three cornerstones that exist in drug development: that's safety, efficacy and quality. And throughout this talk and my final one, I'll try to align our programs to those cornerstones.

[Slide.]

The divisions--in green, on your left--represent our quality side in OTR, and on your right, in blue, represent the biology side--or mostly safety, a little tiny bit of efficacy.

About 75 percent of our staff is in the left side, under "quality," about 25 percent is on biology. I'm the director of the Laboratory of Clinical Pharmacology, and also Acting Director of Applied Pharmacology.

[Slide.]

There are three research programs in the Laboratory of Clinical Pharmacology. For those of you who've served on this committee in past terms,

we started a metabolism and drug-drug interactions program in the mid-'90s. Our goal was to interpret what was then a barrage--a virtual avalanche--of data from in vitro systems, trying to predict interactions between drugs, between drugs and food, on the basis of metabolic pathways. This has been a program in concert with the review staff that's resulted in the production of several guidances--I'll mention that in a minute.

A more recent project is hepatotoxicity. Hepatoxicity, or idiosyncratic hepatotoxicity in particular, has been a major cause of drug withdrawals--we're actually trying to use our expertise in metabolic processes and apply it to an extension into liver toxicity. We'll come back to that.

And, finally, the only project, really, in the office that's related to efficacy, we're looking at PET imaging for early therapeutic assessment. It generates a number of interesting consultation reviews, and it's really and extension PK-PD issues that clinical pharmacology

subcommittee--this group--deals with regularly.

[Slide.]

I don't need to tell this audience that adverse drug-drug interactions are a major headache, and have been a major problem. I think we have a very, very simple goal in approaching this problem, and that's to improve the efficiency and design of human clinical trials to eliminate--or at least minimize to the smallest possible degree--the potential for drug-drug interactions.

They're relatively easy to find. They're relatively easy to predict in advance. If you can triage the worst ones--the potentially worst ones in vitro, and study them in vivo, then you can gain an incredible amount of confidence, rather than looking under every stone for another drug-drug interaction.

[Slide.]

In addition to our work in dealing applications that come from drug sponsors, we also work with the National Cancer Institute, which has

its own drug development pipeline, and we have a memorandum of understanding to help them learn the technology of drug metabolism so that they can apply it in their pipeline. One of their employees actually works in our laboratory on theses techniques, and we've also participated in some of their Phase I trials by analyzing the drug and metabolism in vivo in their first in-human studies.

[Slide.]

This is the only flow diagram I'll show. This essentially describes a decade-long process in which we do metabolism studies using human liver, in vitro in our lab. That led, initially, to a guidance on how to do relevant in vitro drug metabolism experiments. That guidance was enhanced by the review experience, particularly from the Office of Clinical Pharmacology and Biopharmaceutics. We then extended that to the in vivo situation, giving a guidance for industry on in vivo metabolism, drug interactions designs, and that also built upon collaborate clinical studies--when we were able to do them--as well as

the metabolism-based drug-drug interactions that we were able to study in the laboratory. And these guidances are currently being updated in Clin Pharm subcommittee of this parent committee, has been active in reviewing it, sort of stage by stage in some of the new areas.

[Slide.]

Hepatotoxicity, as I mentioned, is really and extension of our expertise in drug metabolism, because it's been known for decades, now, that some of the most troublesome liver toxicities arise from reactive metabolites--not from the chemical that was swallowed or injected into the patient, but from a metabolite that was formed right in the liver, and the liver being the place where the metabolite is first form, is also the first site of potential injury.

So we're using our expertise in understanding metabolism, to look specifically at reactive metabolites. We aren't doing this in isolation in the laboratory. John Strong, the PI on this project is on FDA's steering committee.

There's a joint program with PhRMA to meet regularly and discuss hepatotoxicity issues together.

[Slide.]

Here's an example of the analytical procedure that John and his group use. Glutathione is the universal sponge for sweeping up reactive metabolites as they form. So, by radio-labeling the intracellular pools of glutathione, we can look at what grabs onto it after the end of an incubation with an unlabeled drug, and we've labeled the reactive metabolite by its linkage to glutathione--almost an operational definition of what is a reactive metabolite: it's something that wants to get together with glutathione.

Using the prototypical liver toxin, acetaminophen, we were a bit surprised when we did an inter-species comparison: it's a known hepatotoxin in homo sapiens and in the rat. And what we found is that the rat and the human have one very large peak, eluting at about 13 minutes on the HPLC tracing. The rat also has a second peak.

I think the important thing is not to get distracted by inter-species differences in this case; just a take-home message that, while you can see it in rodents, since we have the ability to do these experiments in human liver in vitro, that's where the focus of our experimental work ought to be.

[Slide.]

Just a minute t talk about efficacy. PET imaging is intended primarily to look at an early evaluation of drug action. And our involvement has been to try to encourage innovation into this process.

Those of you who've looked through your background materials in the launch document from March of 2004, "Noninvasive Functional Imaging" was highlighted in the roll-out as one of the areas in which FDA and industry have agreed to work together to try to maximize its potential for finding the winners and losers relatively early, streamlining drug development.

We will be announcing a joint meeting with

BIO and with PhRMA, and with the Drug Information Association early in 2005 to convene the community of imagers and therapeutic developers to see how the two can bring their tools to the table.

[Slide.]

In terms of why we're doing it, FDA, CDER, has a very long history--as many of you have heard in your service on this committee--in using pharmacokinetic and pharmacodynamic principles and their application to regulatory decision-making.

The disappointing thing, scientifically, is we're always looking at extra-cellular fluid. We do the absolute best we can with what we've got to measure, but when it's just the circulating plasma, we're only seeing part of the problem.

And the mechanism-based activity of the drug is inside the cell. And the ability to see distribution of a drug inside the cell, its interaction with receptors, enzymes and transporters, is more like what's done in drug discovery, in terms of figuring out why this drug was picked. So if we can find out in vivo [sic]

whether we have the right concept being applied in vivo and select the dose, it could make our downstream work a lot easier.

[Slide.]

A good example of this is a drug that was reviewed by FDA's GI drug Advisory Committee last year, and recommended for approval. This is a drug called Emend, or aprepitant, from Merck. It's intended for the reduction of chemotherapy-induced nausea and vomiting.

And this is the classic curve that this committee and other Advisory Committees--and our review staff--are usually faced with in drug development. The y-axis is a measure of activity--Phase II data, not Phase III data--and the x-axis is some plasma concentration of that drug. So there's an attempt made to link pharmacokinetics with pharmacodynamics. And what was found was that at 40 milligrams there was some activity, but it was sub-optimal. At 125 milligrams, we exceeded 90 percent of the activity; at 375, of course, we were up on the shoulder, or

the plateau, of the curve.

So it was a molecule that certainly showed dose-response, or dose concentration response. The question is: did any of that activity relate to why this molecule was chosen for development? Or is just a me-too that acts by the same mechanism that other drugs do?

Well, Merck Pharmaceuticals is one of the leaders in applying PET imaging to the study of drugs in their pipeline. And this is a tracer map, on your left, of substance P-receptors in the living human brain. And the color scale is that red is the hottest concentration of receptors, followed by yellow, followed by dark and then lighter blue and then darker blue.

So that's the phenotypic map that can be measured prior to treatment, or in a placebo arm. And it's consistent with what's seen in the human brain at autopsy--except that this subject is living.

Subsequently, as you move across to the right, the next image is what happens at 40

milligrams. 40 milligrams--we would interpret this image as--is very effective at blocking the receptor, so that when we give a probe--a radio-labeled positron-emitting probe for substance P, it no longer can stick to the receptor, and therefore we don't detect it--non-invasively.

As we go up to 125 milligrams--the middle image--there's a little bit better blockade. If you do quantitative analysis, you can see additional blockade. But clearly we're reaching the plateau. And 375--and one higher dose, shown on the far right--don't get you any extra benefit.

These information are supportive to approval. The drug was recommended for approval by the Advisory Committee, and approved by FDA, on the basis of its activity in randomized Phase III controlled trials. But the reason these data were supportive, and presented to the Advisory Committee were twofold. First of all, they relate the activity of the drug, at a particular dose, to the presumptive mechanism of action. And, number two, they permit the lowest possible dose to be used.

Well, we all are familiar with that concept: to maximize the therapeutic index you want to minimize the penalty, in terms of adverse effects. It turns out that the higher you go with this drug--just like others--the more baggage you bring in terms of adverse reactions.

In this case, there's a serious increase in drug-drug interactions because aprepitant induces and inhibits many metabolic systems. Since these patients, by definition, are going to be taking a bunch of other drugs at the same time, minimizing drug-drug interactions by using the lowest possible dose, consistent with preserving as much anti-emetic potential as possible, helped in choosing.

So, on the basis of this linkage of imaging studies with Phase II data, the sponsor chose 100 milligrams as their dose for the randomized Phase III trial, and an add-on trial, and it showed superiority in a placebo-controlled test--an example of what we think is generalizable in many therapeutic areas. So much for Clinical

Pharmacology.

[Slide.]

In our Applied clinical Pharmacology Lab--which also might be called "Pre-clinical Safety"--one of our elements is molecular toxicology. And, like other labs at FDA, and in university labs, we're very interested in microarrays for their potential to show us a broad range of signals, good and bad--in the case of pre-clinical safety, early indications of possible toxicity.

However, from a regulatory standpoint we're very concerned--just like most of the community is--in the chip-to-chip, platform-to-platform, reliability and consistency of microarrays. So microarrays are very impressive as an 11,000 gene, one-page readout of most of the relevant genome, but it's not the quality of the image--the "awe factor" that we're interested in. We want to know that if we take that same sample and do the next 10 chips, with the same platform, will we get the same picture? If we go from an

Affymetrix platform to an Agilent platform, will we get the same kind of readout?

Those are the questions, if we're going to make regulatory decisions on the basis of these kinds of data, those kinds of cross-platform and chip-to-chip reproducibility are what's important.

We can't do this by our own. We have three people who are involved in this project. So we partnered with the platform makers, the users of these, and we're doing multi-laboratory , inter-laboratory comparisons of standards. And it seems to be proceeding at the right pace.

[Slide.]

The second important aspect is not just does the picture look the same, but how do you analyze the picture? What kind of statistical tests for robustness can you apply? And there, we've enlisted a very good partnership with our internal CDER statisticians--Bob O'Neill, who joined us earlier in this meeting--and Bob's been a very effective advocate, among the statisticians across all centers at FDA, to form a partnership

between statisticians and biologists. So we'll generate all the data that will help them develop tests for figuring out multiple comparison, correction factors, and all the things that they do behind the scenes. And they'll help us develop metrics for figuring out how reproducible the quality is.

[Slide.]

In terms of gene markers of toxicity, not surprisingly, we're interested in cardiotoxicity, renal toxicity and, more recently, differences in pediatric toxicity versus adults.

Again, this group is not acting in isolation in our ivory tower in the White Oak laboratory; closely connected to the Senior Science Council--Associate Commissioner Alderson's group; and several of us are on the Inter-Center Working Group on Pharmacogenomics, chaired by Larry Lesko.

We've had two joint workshops, between FDA and PhRMA, that we've participated in, and the third one is in planning for 2005.

[Slide.]

In preclinical biomarkers--"biomarkers" appears throughout the Critical Path document--what we're interested in is trying to zero in on those clinical toxicities that are particularly hard to monitor or only develop late in the course.

And, traditionally, this has been done--this is hardly a new field; we call it different things--but biomarkers, in the past, because of the technology, have been one at a time events. Well, now that we have, you know, multi-channel arrays of various sorts, coming from olmics, genomics, proteomics, how do we bridge the way we did these things in the past to the way we do them in accelerating in the present?

[Slide.]

Well, anthrocyclines, such as doxorubicin are known to cause cardiotoxicity. The slide at the left, which is doxorubicin by itself, compared to the slide at the right--doxorubicin plus dexrazoxane--which is a cardio-protectant, we don't need to be a histopathologist to see that there's a difference, but we do have to have a piece of the

heart. And although you can get a piece of the heart for valid therapeutic reasons, it's clearly a difficult way to search through biomarkers. We'd much rather have some kind of serum test.

[Slide.]

And, sure enough--for those of you who've been following the New England Journal of Medicine and other clinical papers--the troponin series has been recognized--in fact, has been declared in several recent articles--to be one of the major breakthroughs in monitoring cardiotoxicity in human beings.

Now, this particular study that's in front of you this afternoon is looking at troponin T levels in rats. So we took the signal from humans, went backwards, in this case, to see whether we would have picked it up a priori, or in advance, rather than after the fact. And what we find is a relationship between the cumulative dose of doxorubicin on the x-axis, and the serum troponin T circulating in the body.

[Slide.]

Well, that level of cardiac troponin T in the serum does correlate very well with the cardiomyopathy score, scored by a histopathologist. So it looks certainly like it has the characteristics of a good biomarker. But it's one thing.

Is there some way to generalize this and look more broadly?

Well, using expression arrays, we've looked at a variety of different pieces of the heart--pathways in the heart--that are known to be affected by anthrocyclines, or have unknown effects of anthrocyclines.

So, certainly, cardiac muscle function and structure, you can imagine, is adversely impacted by doxorubicin itself, and yet if you look at the far right column, dexrazoxane has a protective effect there.

We were unsure about fatty acid metabolism and glucose metabolism, some aspects of immune response. We get some mixed signals there--all of which show changes in the treated animals with

doxorubicin, but in animals who get the same dose of doxorubicin--in the middle--and get the dexrazoxane as well, most of those changes are modulated. The control arm is the right arm for dexrazoxane by itself. And finally, it's not surprising that something that's done this much structural and functional damage also has stress-induced genes that are highly overexpressed.

[Slide.]

One last example, from the safety domain--recently, across many different therapeutic areas, the phosphodiesterase inhibitors, among sub-families 3, 4 and 5, as well as other vasoactive drugs, have been shown to have bleeding problems: vasculitis, vascular injury problems. And although there are species differences across the mammalian empire, rats, dogs, primates and sometimes mice, have shown this phenomenon. However, the only way you can see it is with invasive testing. So, in keeping with our mission, we were looking for biomarkers that might be associated with it.

And a number of them have been studied. Again, we're more into one at a time, or a few at a time. We had a half dozen; here's four that fit in a slide and might be still readable--

[Slide.]

--in which we can see a progressive increase in circulating markers when the vascular histopathology score is going up as well.

So, treating rodents with a variety of phosphodiesterase inhibitors causes circulating biomarkers to go up, and that increase in marker is associated with the invasive test, which is looking at histopathology.

[Slide.]

I guess the bottom line is that these biomarkers represent a potential new tool for evaluating preclinical safety, and as important an endpoint as that is, I have to ask whether it could be extended into humans, as well. And I'll talk about that later in the day.

[Slide.]

In summary, on the biology side of the

Office of Testing and Research, our programs in biomarkers, pharmacogenomics, noninvasive imaging and drug interactions are certainly the template, or the scaffolding that you could develop a Critical Path Initiative around. We feel very well aligned and prepared to charge into the Critical Path Initiative projects that we think are quite harmonious with its goals.

CHAIRMAN KIBBE: Questions.

[Pause.]

I don't see anybody jumping to the microphone--go ahead.

DR. KOCH: I guess it's always in the definition of "noninvasive," but with the PET, you still need to inject the radioactive, short-lived isotope. But that's noninvasive?

DR. COLLINS: Well, I guess my FDA training would have me modify it to "relatively noninvasive."

DR. KOCH: Oh, okay.

[Laughter.]

DR. COLLINS: We also included MRI

techniques in that regard. And if you don't have to use a contrast agent--if you're doing the standard T1 and T2 kind of paramaterization--you actually do that--the only invasiveness is a magnetic field. And it's--you know, particularly where we come from, we're certainly not going to blow off the risk of these kinds of things. But we can quantify those risks in terms of other everyday life activities. The radiation in a PET image is less than that of a conventional chest x-ray, and it can be made lower with more specific detectors that are being detected now.

I forgot how many airplane trips back and forth to Denver it would be equivalent to; the radiation that you get at 35,000 feet.

So there are additional, incremental risks that are undertaken, but in the context of everyday risk, the local IRBs, human subject committees, and the FDA have said, well, the benefit to society versus the minor risk is okay.

But there are very strict dosimetry limits on the amount that we can give as a radio tracer.

CHAIRMAN KIBBE: Anybody else?

[No response.]

You seem to have done a successful job of presenting information.

And now we have Dr. Buhse.

DR. BUHSE: Okay. I'm Cindy Buhse, Director of Division of Pharmaceutical Analysis. And as Jerry mentioned we are on the quality side of OTR labs.

My lab is mostly responsible for looking at analytical methods that are used to test drugs. And so my labs mostly made up of analytical and physical chemists. And I'm going to go through some of the programs we have.

[Slide.]

Let's see. Programs we have to support the Critical Path Initiative--some of these you've heard of this morning from John Simmons and Lawrence Yu, because a lot of what we do supports ONDC and OGD, in terms of trying to help them determine how we can characterize novel dosage forms and complex drug substances, not only to help

ensure we have the correct testing to approve a generic drug, but also to ensure that we have the right testing to approve changes in manufacturing in innovator drugs.

We also have programs to measure and identify micro and nanoparticles in drugs, especially--it's often easy to measure the size of a particle before you mix all your excipients and drug together, and once you have a drug all mixed together, what does that do to the particle size? And we need ways to take a look at what's going on in actually, final drug formulations.

We also establish--help establish appropriate surrogate measurement techniques. Lawrence talked quite a bit about this, and dissolution is a big thing that goes on in our lab in this area.

We also work a lot with the Office of Compliance on drug authenticity and anti-counterfeiting techniques. It's an issue--I think if you watch the news at all--not only, like Amy mentioned, in biologics, but its also an issue

with regular oral dosage form drugs.

And then we also--the last two, I'll briefly go over--process analytical technology, research we're doing, and some chemometrics, as well, that ties into that. We're working with DPQR--Mansoor Kahn's group--on those programs.

[Slide.]

To start off with the characterization of novel dosage forms--some of the work that's currently in our lab are things I think you've already heard about from ONDC and OGD. We have a program on liposomes, trying to characterize them after chemical and physical change; trying to determine how to--what analytical techniques work best to detect changes in liposomes. And we have a program with DPQR, as well, to take that a step further and see if we can use cell-based assays to see how these changes in the liposomes can be detected in the cell-based assay.

Looking at transdermals--people call them "patches" as well, patch products--and their adhesive strength. How can we characterize the

adhesive strength and assure we have an analytical method that can be used to no only compare a generic to an innovator, but also can assure the quality of a patch before it's released for sale.

John Simmons mentioned conjugated estrogens. We have some LCMS techniques we've been running. He showed some of that data. And we're trying to improve those methods to make sure they're very reproducible and can be used to compare innovator to generic, or to compare an innovator product after a change.

We also do some work with protein products, trying to look at different analytical methods to detect aggregation and degradation, and assure we know the exact molecular weight and distribution of protein products and can characterize those.

Some of the regulatory accomplishments we've had in the past in this area include input into conjugated estrogen guidance, which is currently out.

[Slide.]

This is just to give you an idea of the kind of work we're doing on the liposome project. We're looking at two different types of liposomes: Pegylated and the convention--in fact doxo--the very drug Jerry was just talking about, up there in a liposome form.

We're looking at different stress conditions, and then looking at different analytical methods to determine how the liposome was affected. Was the actual drug substance itself affected? Or was the liposome affected both in the lipid composition and in the amount of drug that's encapsulated in the liposome?

And we determine what stress conditions will give us a small amount of degradation, and then Mansoor Khan's group will take those degraded liposomes and see how they react in a cell-based assay, see if we can see differences in their uptake.

[Slide.]

Patches--there are different types of patches out there on the market, and we're taking a

look at both kinds when we look at adhesive properties.

One has actual drug in the adhesive--the adhesive and the drug are mixed together and you actually get your dosage by the size of the patch. And then there's also reservoir-type patches. And if you start looking into adhesive properties--and we actually are jointly working with CDRH on this, as you can well imagine, with things like band-aids and medical tapes. There's a lot of variables to look at when you're doing test method development on adhesives. And I've listed some of the variables down below that we're looking at to try to come up with a method that could be reproducible for patches.

[Slide.]

In terms of measurement and ID of micro and nanoparticles, some of the projects in our lab include looking an some of the sunscreens that are currently being marketed as having nanoparticles. We're trying to look at seeing what techniques can be used to evaluate the size of these particles

once the sunscreen has been formulated.

And likewise, in nasal sprays, we want to know what is the particle size of the active ingredient once it's been mixed together, especially nasal spray suspensions. And I'll show an example of that in a second.

We've also done some evaluation of Andersen Cascade Impaction, which is used to determine fines--trying to determine how to improve that test method. It's very variable, and are there other options to using Andersen Cascade Impaction to get a handle on fines in nasal sprays.

Some of the regulatory accomplishments that have come out of our lab included input into the nasal spray BA/BE guidance; and also we've done some measurement work with cyclosporine particles and helped ONDC and OGD with that.

[Slide.]

This is just an example of some of the work we've done on nasal sprays. Here's some raman chemical imaging. And you'll see--I guess it's all the way on your left, up at the top, you have a

Brightfield, just microscopic image, of the nasal suspension. You can see a lot of different particles there. It's hard to tell which particles actually are active. So if you're trying to determine a particle size of your active within this formulation, it's tough to tell just from that picture.

You can kind of tell--you look at MCC, kind of is that rod shape there. However, if you actually can take the Rama spectra of each one of those particles--which is what's shown just below that, you can see that the spectra's very different at each one of those particles, and you can look for the Raman spectra of your actual active drug to determine which one of those particles is your active drug. And that's what's shown down at the right--at the bottom. We're determining from the Raman which one of those particles in that image is actually the active drug. And you can see that there's two of those particles that are active drug, and there's a little bit of an active drug, maybe, attached to some of that excipient.

And from that we can then get the particle size of the active drug within the formulation, and we can also get a feel for maybe if the active is maybe sticking to some of the excipients, which may actually change its actually size from what you think you might have put it, from the formulation.

[Slide.]

Establishment of surrogate measurement techniques--we've done quite a lot in the last year on dissolution, trying to do quality of drugs. We've worked with Office of Compliance on the malaria drug mefloquine to try to figure out why it was or wasn't working in the field, for the military. And we've also done some work with megestrol acetate suspensions, trying to compare generic to innovator drugs, and figuring out the best dissolution test method to use for that.

In general, we're taking a look at dissolution testing because it is heavily used--as Lawrence said--not only for quality control, but also to try to--for bioequivalence, as well. And so we're trying to make sure that the actual

dissolution test methodology can be as consistent as possible.

For those of you who do dissolution, you know it can be a very variable method.

[Slide.]

This is just some information on the calibrator tablets that are issued by USP to check set-up of your apparatus. And you can see that the limits on the calibrator tablets are very high--28 to 42 percent is the range that you can get for the Lot M. And lot N which was after that, was 28 to 54. And Lot O is currently out, and is proposed to be just as wide, if not wider, than Lot N.

So if you use a calibrator like this to test your apparatus set-up, you can see that any variability that you're seeing in your test method potentially could be due to apparatus set-up, because you're not going to be determining it from this calibrator tablet, because it's just too variable. And so our lab is looking at alternative ways to ensure set-up and reliability of dissolution apparatus, other than using calibrator

tables.

[Slide.]

One of the areas that I think has become very important lately is just anti-counterfeiting techniques, and ways to ensure that the drug you're taking is the actual drug you thought you bought. And so our lab takes--keeps a close watch on technologies that are out there for counterfeit, and even to see how they can apply. We've been involved in several projects with the Office of Compliance to ensure the quality of not only the active pharmaceutical ingredients, but also foreign Internet samples.

So we've tested both of those in our lab. And we used conventional techniques--like HPLC and GC--looking for impurities, etcetera, to see whether the drugs are the same as the U.S. equivalent. But we've also taken a look at new technologies, because some of these can be very powerful, much faster ways to detect counterfeit, or can actually show us new--maybe give us clues as to where drugs may have come from if they are

counterfeit.

[Slide.]

As an example, I was just going to show a little bit ratio mass spectrometry. This is a technique which uses stable isotopes to try to detect where chemicals may have come from, and also to determine if things were made in the same plant or not.

This is a plot of the stable isotope of carbon--which C13, versus C12, and oxygen, which is O18 versus O16. And you can see that Naproxen, manufactured at different places in the world, and different plants in the world, cluster together, in terms of their stable isotopes, and that's because stable isotopes aren't the same around the world. And when you manufacture a product, your stable isotope composition within that product is dependent on the raw materials you use, where those raw materials came from in the world, and also on your manufacturing pathway. And so it can be a powerful technique. You can see, if you have a drug, and you can test it by IRMS, and then

determine potentially which plant it came from.

[Slide.]

In terms of PAT--as in anti-counterfeiting, we try to take a look at the technologies that are out there, either new technologies or maybe new to the pharmaceutical industry, and try to determine how they might be used for PAT; what some of their limitations or benefits might be so we can be in a position to advise ONDC or OGD as needed.

We have a couple projects in our lab taking a look at coating composition, how that affects the ability to see what's going on within a tablet, and also taking a look at excipients and excipient-drug interactions within spectroscopy, and how that affects the ability to use spectroscopy for PAT.

[Slide.]

As an example I wanted to show you Terahertz spectrometry. Terahertz--this is between infrared and kind of your microwave. You can see up there on the spectra on the right, there. And

one of the benefits of terahertz, it's like NIR; it's non-destructive. But it also is a lot more penetrating. The NIR can go deeper into a tablet or into tissues.

So it's being looked at, not only for quality control of drugs, but also as imaging of biological tissue, especially skin cancers.

And I just want to show you a little bit of the spectra we've gotten. These are acetaminophen tablets. They're from 65 to 135 mgs, and you can see that the terahertz spectra, which is the one on the left--it's not much features there. I mean, you would probably look at all of those and say that they looked pretty similar. But if you take that data and you run it through some parametric programming, and compare it to content by near-IR, you can see you get a very good fit between the terahertz and the near-IR. But the good thing about terahertz, it would have the potential to go--to look past a coating, or to look deeper into a tablet than near-IR.

The terahertz here was actually done with

transmission. So by detecting the radiation through the entire tablet, and near-IR often you do reflectance.

[Slide.]

Chemometrics is another project that we're doing with DPQR, trying to understand the chemometric software packages that are out there. If we're requesting people to use PAT, and to use more multivariate techniques, we want to understand what their limitations and benefits are, especially for model building--pre-treatment of data, things like that. We want to be able to provide expertise in that area.

Just as an example, the kind of things that we've been doing. Here's some near-infrared of those--actually the same--acetaminophen tables that I just showed you with terahertz. But this is all with near-IR. On the left is near-IR reflectance, which is the full range of the spectrum, from 4,000 to 10,000 forcipical centimeters in the near-infrared. On the right side is transmittance--okay? So this is where

you're trying to go actually through the tablet. You'll see it's a little noisier in transmittance, and you can actually only use about 8,600 to 10,000 because of the noise.

However, depending on how you treat the data--you can see underneath the reflectance we have--we've taken a second derivative, and we get a good correlation between the near-IR and the content measured by HPLC. However in the transmittance data, we don't need to do the second derivative. We can take the direct spectra and get the same time of correlation with the content measured by HPLC.

[Slide.]

I just wanted to put this up because people talk about the St. Louis lab, sometimes. That's us, I guess--Division of Pharmaceutical Analysis. We are the only CDER lab located outside of Maryland, so we have a small group of people at White Oak, with Jerry Collins and Mansoor Khan. But we also have our larger laboratory in St. Louis. And so a lot of our interactions occur by

video-conference and telephone. But we still manage to get quite a bit done out there.

So--hopefully the Cardinals will come back in the next two games because, of course, everyone's very depressed about that out in St. Louis. So I'm not sure there's much work getting done in the lab right now, after last night's defeat.

[Laughter.]

So--I'm happy to answer any questions about the Critical Path Initiative.

CHAIRMAN KIBBE: Questions? Michael?

DR. KORCZYNSKI: This is more or less a comment. And I don't know whether you could directly answer this--but, pharmaceutical analysis--as you were speaking I was wondering: most of the products that we're discussing are, indeed, sterile products.

So is there a counterpart to your activities in the microbiological areas, such as a laboratory investing microbiological analytical methods for even investigation of counterfeit

drugs, or bioterrorist activities? Is there some type of microbiological analytical counterpart to pharmaceutical analysis of products?

[Pause.]

Or maybe it's resourced out. I don't know.

DR. HUSSAIN: Well, I think much of that is done in our field labs. And Amy--and I don't know whether we have a focused effort on microbiological methods, but counterfeit efforts on many of the injectable protects and OBP are being carried out, too.

But, we actually do not have a very focused broad quality microbiology lab within OPS.

CHAIRMAN KIBBE: Go ahead--Mike?

DR. KOCH: Yes--question, Cindy--on the surrogate dissolution--

DR. BUHSE: Mm-hmm.

DR. KOCH: --you know, we heard this morning of the different pHs, and time and different things that go on there.

Over the years has there been, in addition

to the USP standard dilute hydrochloric acid approach, has there been a way to simulate the process, to try to come up with a dissolution test that goes through a low pH, followed by neutral pH, etcetera--to actually try to simulate.

DR. BUHSE: There's been a lot of research done on dissolution, and there's a lot of research in the literature and in academics. They have--one of the dissolution apparatus is like a flow-through apparatus, rather than the vessel, and some of the studies done on those have been the type that you've talked about. There, you don't recirculate the dissolution media, you just continue--and you can continue flowing it through the tube, and you've got the actual pharmaceutical suspended in the middle of the tube, and you can change the media as it goes through--things like that.

So there are research programs out there like that, and we're reviewing those and seeing how they might be applicable--or maybe more applicable than the vessel method.

CHAIRMAN KIBBE: Go ahead.

DR. MORRIS: Yes, just a question on the chemometrics--looking at the well-executed, but relatively traditional chemometric approaches in evaluating the packages that are out there.

Looking at cross-process chemometrics in sort of process-vector type work, or multi-block systems to try to take into account more than a single assessment of a product, as opposed to looking at the product train?

DR. BUHSE: I guess--maybe Ajaz, who knows a little bit more--

DR. HUSSAIN: Right--no, I think much of the internal work has been focused on what we can have.

DR. MORRIS: Sure.

DR. HUSSAIN: Because we're hoping the CRADA with Pfizer, I think we're just starting to get in the process and so forth--I think our interest would be to get at process signatures and so forth. But I think for that we need to have a collaboration where we have that.

Mansoor is actually setting up the

manufacturing lab. And so once that is set, we will have access to that. But most of the work we're doing right now with in-house data is based on chemometrics for products that we have our hands on.

DR. BUHSE: Yes, and we've done a little bit of that. Some of the data I showed you was for one--like, for instance, for one compression rate. We have similar tablets we've made--exact same formulation, at different compressions, different excipients.

So we, you know, try to throw more variables into it. But I think some of the CRADA and manufacturing efforts--make it more--give us more the ability to do further work in that area.

I think Judy had a question.

CHAIRMAN KIBBE: Yes, Judy had a question.

DR. BOEHLERT: Well, I'm down here in the corner.

This is sort of a general question-comment. It applies to you and to several of the more recent presentations this afternoon.

You have a number of research projects--liposomes, characterization, adhesive nature transdermal. To what extent do you interact with industry? Because industry is also working on these same factors, and looking at adhesive strength, looking at the stability and characterization of liposomes.

And, you know, I don't want to see people going in two different directions to come up with two different ways to do the same thing. So is there synergy between what you're doing and what the industry groups--or maybe even the academics are doing?

DR. BUHSE: Yes, some of the projects we do work extensively with industry; with the patches project we've been working with--I think I mentioned CDRH, our other center, but we've also been working with 3M extensively, because they have such a knowledge of adhesives, and they also actually manufacture quite a few of the adhesives for patches--as it turns out.

So, in some cases, we do work with

industry. A lot of cases we're not really able to because what we're doing is trying to compare, perhaps, two different products, or a generic and an innovator, and there starts to become, you know, some issues there where collaborating may be more of a problem.

CHAIRMAN KIBBE: Follow-up, Ajaz? Go ahead.

DR. HUSSAIN: no, not follow-up. I think I just wanted to sort of emphasize--John Simmons had mentioned the rapid response.

A lot of the activities in the St. Louis lab are getting to solving problems that we face. For example, the adhesive issue came up through dramatic failures in adhesive performance on--we manage, in the Office of Pharmaceutical Science, a Therapeutic Inequivalence Action Coordinating Committee. And then from the MedWatch, from the consumer complaints--we were receiving a lot of failures of transdermal systems falling off.

And then we looked at that and said we actually do not have a good method, which is also

part of the stabalating program for many other products. So that was an outgrowth of that.

And liposomes, for example--one of the challenges was we were setting dissolution specifications on liposomes--I'm not kidding. So we said, "Let's understand some of that," and so forth.

So, a number of projects that Cindy does--immediate answers that are needed, and that is a very critical element. So you have to keep that in mind. So that's a very important lab, from our perspective, in a sense, because immediate answers are needed for John Simmons' Prussian Blue-type work, and so forth, and so forth. So that's--I just wanted to clarify that.

CHAIRMAN KIBBE: Anybody else?

DR. BUHSE: Quick questions?

[No response.]

CHAIRMAN KIBBE: I guess you're off the hook.

DR. BUHSE: I guess it's on Mansoor.

CHAIRMAN KIBBE: Dr. Khan.

DR. HUSSAIN: Just as he comes on board--he is new to FDA. So he came from academia. So he's--

CHAIRMAN KIBBE: You're asking us to be nice to him? Is that what you're doing?

DR. HUSSAIN: Yes, that's it.

[Laughter.]

DR. KHAN: Good afternoon. It's quite a challenge to stay motivated and speak in the afternoon, but I'll try to do my best here.

I'd like to thank Dr. Webber and his team for giving me this opportunity. I would like to thank the Advisory committee for your leadership and the important role you play in this process. I'd also like to thank the audience, who have been extremely patient since morning--I've been noticing. So--audience.

Most importantly, I would also like to thank my colleagues from the Division of Product Quality Research. Some of them are here, and some of them that are not here, but they have given me some of the slides to share with you, just to show

what goes on in the Product Quality Research.

[Slide.]

I will just briefly go over the outline. People do ask me--I'm also new here, as Ajaz just mentioned--that, you know, they asked me, "Okay, what's the mission? What do you do?" So I would briefly at least outline the mission and the reason that we have here, then present to you the team, so you'd get an idea of what our division is about, and the current needs related to Critical Path and the cGMP initiatives; some of the future directions; and examples of "design space." It comes about a lot, and I thinks morning, also, a question was asked about the case study. I may not be able to provide the case study, but at least I can provide some examples of that one. And then some questions about that. Okay?

[Slide.]

The teams--sorry, the mission first.

Advance the scientific basis of regulatory policy with comprehensive research and collaboration; focus/identify low and high-risk

product development and manufacturing practices; share scientific knowledge with CDER review staff and management through laboratory support, training programs, seminars, and consultations; and foster the utilization of innovative technology in the development, manufacture and regulatory assessment of product development. Basically, we would like to stay aligned with OPS and the CDER missions.

The vision--we want to be recognized leaders in providing support for guidance based on science and peer-reviewed data; well trained staff and state-of-the-art product quality laboratories that is capable of providing any information sought by reviewers, industry and the FDA leadership.

Culture--the way we live and act--one of cooperation, mutual respect, synergy, professional development with life-long learning opportunities. Basically, this slide I derived from some of the internal presentations. I just wanted to go over it so that we are all on the same page.

[Slide.]

The division, we have about 19 scientists

currently working on this. We have three teams. The fourth one is in the making: the pharmaceutical/analytical chemistry team; we have a physical pharmacy team; a biopharmaceutics team; and a novel drug delivery systems team.

So I'll briefly go over what they do, and share some of their slides with you.

[Slide.]

Pharmaceutical/Analytical Chemistry projects--we have team leader Dr. Patrick Faustino. He has done some work on this Prussian Blue--basically, safety, efficacy and product quality studies. John has presented to you this morning some of those studies. And basically that laboratory work was done in a DPQR.

Then we have the shelf-life extension program, where we have the stockpile of drug with the U.S. Army, so we look at some of the stability issues of those drugs. And, then, very recently they've also worked on isotretinoin--some of the bioanalytical and kinetic studies they have done.

Basically I'm just going some of the

current work that is being done, and what we want to do to make changes, with your recommendations on this.

[Slide.]

Just one slide--he has already shared these things with you, but I think this is just the effect of pH we have seen, because this is a compound of high interest--radioactive decontaminant. It was releasing some cyanides we have seen that the release of cyanide is much less at a certain pH--I was just focusing here--that the release of cyanide is much less at certain pH, so safety at a certain pH--you know, it's much safer. And then the efficacy--we have done some binding studies of radioactive cesium. Also we are working on thallium on this one. So the binding studies we have seen as the pH goes up, the binding is more here on there. So this gave us some idea about his compound.

[Slide.]

The next team, the biopharmaceutics team, headed by Dr. Donna Volpe. And it's a small team.

If we want to go in the area of bioavailability and other issues, then I think this team needs to be expanded a little bit.

They have broad activity on the BCS guidance. A question came up this morning, also, about the extension of this BC guidance. Donna Volpe is working actively on these things.

They have also worked on--there was some bioequivalence issues of levothyroxine sodium products. So we have looked at the stability of this. It was a huge project. A lot of people were involved with this. We have just completed that project and the final report is about to come out on that one.

We are looking at the effect of cyclodextrin, as well as some other excipients, on the permeability of certain drugs. Dr. Volpe has created a huge database where the permeability of certain commonly studied drugs--like atenolol, some metopralol--and, you know, we also looked at the permeability of mannitol and the various factors affecting the permeability of that drug. So we

have created a database of that.

And some uptake studies--I think Cindy mentioned just some time ago about some of those uptake studies of liposomes. So this is the work which Donn's work group is doing.

[Slide.]

Just to give you an idea--I think that this question came up about, you know, moving this Phase II--BCS Class III drugs in the direction of getting bio-waiver. This will give you an illustration that if you have a high permeability drug--you have a metapralol drug, a high permeability drug, you get these two different excipients there. There was no difference.

But if you change the excipient, where we have this osmotic agent here--the sorbitol--then you see there's a tremendous difference in the availability. So this needs to be sorted out more--you know, to seek the bio-waiver. So this group has helped us study some of those things.

[Slide.]

The next group--the physical pharmacy team

that we have: Dr. Lyon, Robbe Lyon has done a work in the PAT-related issues--the Process Analytical Chemistry, I might say, because Chris Watts keeps correcting us on this "PAT"--the terminology of PAT. But what I'm talking about is mostly the chemistry aspects of this PAT. And then Everett Jefferson is the team leader of that.

And so I will highlight some of the slides. They have given it to me--just to show you what they are doing with these analytical sciences that we have.

[Slide.]

You can see here--this is just with near-IR profile of--

[Moves off mike.][Inaudible.]

This is a lot easier. You are right. Trying to get where the mouse is. It will come sometime? Okay. Okay. All right. Got it here.

So we have these acetaminophen powder here, the avicel powder, and then you have a tablet here. So you see--so we look at the contents of this--the HPLC. We saw the content, we saw the

near-IR, we saw a correlation. I think Ken asked some question as to what you do--what validation, basically. You eliminate one thing at a time so that you get a correlation where you can rely a bit more on that. That's what they've done on this one.

[Slide.]

Same thing we have done with Raman Spectra here. We have it here in the laboratory. We have this Raman spectra. I will tell you how we can use it, later on, in some of the optimization studies. We want to employ this. But at least now we have the procedures in place to do some of those studies.

Raman spectra--similarly, you look at some of these peaks, and then see the correlation. You see the HPLC content we have done with these tablets, and we have correlated with Raman, partial e-squares.

So you can see the correlation here. It's fairly good here in this one, too.

[Slide.]

Likewise, we have also looked at the blend uniformity. You can see, this is a formulation that it clearly shows that this is well blended, as opposed to this formulation which is not well blended. You see the API, you can see that it is not as well blended here.

So if you look at the near-IR spectra, the spectra is very close to each other. You know, it's likely that it's a good blend; you know, they have mixed well. This is separating out. That means, you know, they have not really mixed very well. So it gives us some idea of this mixing.

[Slide.]

Now, hydration--this hydration--Robbe Lyon has given me--hydration is not the process of hydration, it's basically just an identification of a product which either anhydrous, or a monohydrate, or a some hydrate we can detect--whether the product is hydrous, or anhydrous--anhydrous product or a hydrated product.

[Slide.]

The next slide will show we have basically

two brands of product. We have brand 1, a capsule, and then a Brand 2. You can see, this capsule here, it has Core A and Core B. Basically, it has two different cores--okay? And no some Brand 2 has three cores, instead of two cores. Basically they have two of this B core, and one of them is core A.

So if you want to detect how much of it is anhydrous form, or how much of it is in the hydrate form. So they look at some imaging here, and that imaging, basically they are showing that in core A, there's--these are nitrofurantoin capsules, by the way--in core A you have more of the anhydrous concentration. And basically they have estimated it to be 8 percent. And actually, when they have seen it, it was 9 percent there here in this one.

And, similarly, when they did it on this brand, in core B you have seen this is a monohydrate concentration, this has more of the monohydrate concentration. The estimate was 50 percent, but the actual was 40 percent.

So, you know, it just gives us some idea of see the current, and it's not just the drug.

But we can look at the different polymorphic forms of the drugs themselves.

[Slide.]

This is the near-IR dissolution correlation. We have looked at some of the tablets. The tablets were prepared--I think Cindy mentioned some time ago, you know, we had these acetaminophen tablets. I think the next one will show.

These are some tablets. Basically we looked at the tablets. We predicted. We trained the data. This is the training set.

[Slide.]

The one in the blue, and we looked at the correlation. The correlation was .984. And then we have this test data. We looked at almost 72 different tablet formulations, and we saw that it was fairly--especially at a higher dissolution profiles, and a lower level IC, that the curve is off. Actually, if you take some of these data points off, if you take--go for a higher dissolution, when the amount is higher the

correlation might be much higher, if you take these data points off.

[Slide.]

So if I have to summarize as to what's going on currently in the DPQR, this is what it is. We have the Drug Substance--we are characterizing--trying to get the--

[Pause.]

Okay. Trying to get the mouse here--the curser here. Okay.

So, basically, if you have a look--we have drug substance. We are--currently, in the DPQR we have this drug substance. We are characterizing, and the process analytical tools that we have. We have the analytical method. And the biopharmaceutical groups brings some cell culture work. And the drug product--we can characterize the drug product that we are doing here. I have shown you some of the work here that's being done.

And as well as the stability--as I mentioned to you, the shelf-life extension program is going on for some of the drugs of national

importance.

But, as a new kid on the block here in FDA--I know, having worked in academia for a long period of time--for about 12 years I worked in academia--and then after coming here, I wanted to see if what we are doing is enough for us. So what I did, I started listening to the leaders here. I started attending the meetings--some forums like this--you know, the Advisory Committee--your July Advisory Committee, I was here. And then I listened to a lot of presentations of the leaders of the FDA. I got to see what Dr. Woodcock has to say. I got to see what Ms. Helen has to say in HR. I've gone to a lot of their presentations, and I've read a lot of internal reports. I attend a lot of internal meetings, just to see some of the directions.

To give you an idea, you have already seen a lot of Critical Path slides, so I didn't want to duplicate some of those slides. Initially, I had that in the presentation, but I took some of them out, seeing some of the speakers had those things.

But here--you know--because this is a developmental type of research. I think Ken also alluded to this in the morning, as to who will fund this--the level of funding--and who will do this research? If academia doesn't do it, if the NIH doesn't do it, then who else will do it? And the industry doesn't want to share the information.

So at least we will have some work--at least we'll have some data in place so that the reviewers don't have to operate in a total dark box.

Since you have already heard Ms. Winkle's presentation, the support for understanding of--the process understanding and the Critical Path roles is highlighted here in this slide.

[Slide.]

And the internal efforts have culminated, really, in the articulation of this thing in the desired state about ICH, as you can see. I don't know if any other speaker had this, but previously, in the manufacturing subcommittee Advisory Committee that you had here, you had a lot of

people presenting this. Basically, product quality and performance achieved and assured by the design of effective and efficient manufacturing processes; product specifications based on mechanistic understanding; and ability to effect continuous improvement continuous real-time assurance of quality--that's exactly what we want to do in the Drug Product Quality Research. So it becomes easier to expand, it's easier to re-orient some of the programs and expand some of the current programs in BPQR.

[Slide.]

And this is what we intend to do--as I have shown you before. This is the current work that we were doing. Although we had this Chemical Stability here, but we want to look at some of the physical changes there, in that one, too. We want to do that.

And what else we want to do is the manufacturing aspects of this--you know, the role of the excipient, the role of the formulation variables, the process variables, the mechanistic

evaluations, optimization procedure--lot of it may already have been done. We can gather it through the literature, we can gather it through the collaborator, we can do some of the in-house work. But we want to provide this information. We want to provide this training to our reviewers, and we want to update ourselves on these things.

And just to give you an idea: we are talking about--you know, if we want to talk about the process variables--okay?

Now, just taking tablets in the picture, there are so many process variables. You have this mixing, they have milling, then you have your granulation, the drying, compression, coating, packing. Just by mixing you've--you know, the blend, homogenating problems. And just by granulation you might see a lot of problems there. A lot of prime test data is not provided to the reviewer. So to understand that, we need to have some internal programs going so we will have this understanding.

And this we are talking about just a

tablet dosage problem; a dosage form that is so well know--or a capsule dosage form. They are so well know. And when we talk these novel systems that we are getting--

[Slide.]

--by the way, the bioavailability, also, we wanted to either collaborate and do it in house.

The Novel drug delivery systems--we want to have some of this program going in the novel--the nanoparticles--there's a huge, huge area; the liposomes; the sustained release, the modified release; the transdermal systems; the nasal pulmonary path; disintegration; the solid dispersions--basically, we want to have information of going in that direction; we want to have information readily available, and the training that is needed to evaluate those applications.

[Slide.]

Some of the newer projects: the novel drug delivery systems, including nanoparticulates, preparation, characterization, development of in vitro procedures in DPQR laboratories--I will share

some of the data with you. We have already done some work prior to me joining here. I'll share that with you--some science-based projects, with mechanistic understanding.

Process engineering with real time monitoring and modeling. We have this particular equipment--fluid bed--with near-IR probes attached to it so we can monitor a lot of process here in this one.

The SLEP-stability--and there are some repackaging issues. We are working on some of the stability of those repackagings. We want to work on those issues. Basically they are stability-related projects.

Generic drugs--I think Lawrence highlighted some time ago. Tomorrow there's going to be a presentation also. If you have some locally-acting drug, what do you do with that?

Stents--again, combination drugs. You have a device and you have a drug, and you have some issues related to that. We can help in some of thee issues related to that.

We already have CRADAs with companies, and we are going to have some more CRADAs. Somebody asked a question about collaborating with industry. So we are collaborating with industry--and more coming up. And we are very hopeful that we will have some more CRADAs coming up pretty soon, so we will turn in that direction.

Some permeability of these drugs.

[Slide.]

Now let me spend some time here on the design space. I will give you a couple of examples, and then I will also highlight the importance of it. You have already seen that it is important, but I will just share some of the examples with you.

I will share one or two classic examples. This is out of the text--you know, you have some good statisticians, you have some good experts here in this area. All I'm doing is I've just borrowed something from the book, that people have been discussing, and people have been having in the text for a long period of time. So I think the time for

us is just to be able to adapt some of those things, and show their relevance to the pharmaceutical product.

So I will present one or two examples from the literature, and then I will present some examples of a design space in the laboratory generated data that we have here in this one.

Now, here is a scientist--okay? A scientist is trying to work. He has to run a reaction, at a laboratory scale--he has to run a reaction. There are two variables in this one--the time and the temperature. So this scientist is trying to--first of all, it does. So if you have two variables there, first of all it does this, he fixes the temperature here at 225 degrees; he fixes the temperature at 225 degrees. He runs the reaction for a certain length of time. He is basically trying to get the yield of this particular compound.

So, he fixed it at 225 degrees, and then--and he ran it at different times, that particular reaction. He got a yield, something

like 70 or 71 percent, and then he got that yield. And then now that he got the time, then what he did, he fixed the time here. The lower one will show that 1--30 minutes--I can't see very well from here, from this angle--but somewhere here it shows this one, 30 minutes.

So he fixed the time here. Now he ran a different temperatures--okay? So he came up with different temperatures, and he saw that at 225 degrees, basically, he has this yield. So basically he changed one variable at a time, and he got the yield at 71 percent.

But if you have--if you listen to what the statisticians tell us, what they show, if you follow some of the examples that are already out there, we can really perform the very design sort of experiment, the same scientist, when he performs the design sort of experiments--also I might argue that a lot of times you will have less experiments than you will have with so many, you know, duplicates, and triplicates and quadruplicates.

So the same experiment, if we do with a

design set of study--

[Slide.]

--look at what he got. He basically changed the temperature and the time simultaneously. He was basically here in this one--in this design--no matter how many experiments you perform, no matter how many times you do it, you're yield is likely to be around 70, 71 percent, or somewhere in that neighborhood no matter how much time you do. Basically, you are totally out. And somewhere here you would not have gotten it. Somewhere here, you see that he got this 90, 91 percent of the yield for this compound.

[Slide.]

Now I'll stop here for a moment, and I'll change the gear a little bit. Let's assume that we have an identical situation where instead of the yield of this particular compound, we are looking at some other response--this response could be a dissolution response; some percent dissolve in certain amount of time. It could be a bioavailability area. It could be a hardness of a

tablet. You know, it could be any other response that we are looking at.

But if he develops this kind of a strategy--develop some experiments in the laboratory, come up with something like this--but if I have this particular product, if I have this particular response--in the laboratory--I would hesitate to go to the scaling up and to the actual manufacturing, if I have this much a narrow window, then talk about these problems here in scaling up and product manufacturing. Then you say, well, you know, the lab-based data is very different from the manufacturing data. We don't want to do that because it's variable. Yeah, if you are in such a narrow window, any slight change you make, then it's likely to have variability. Then we might fall into a lot of difficulties. We might fall into difficulties of--suppose you have some out-of-spec situation. Then what do you do in a case like this?

Okay? So how do you scale up? Huge problem.

But if you take something around this region--but if our product, if our optimized product is somewhere here in this neighborhood, I would feel more comfortable taking it for scaling up, taking it for the manufacturing, because later on you have--you don't really have a lot of problems of scaling up. You don't really have a lot of problems of out-of-specs. And even if you have some out-of-spec situation, you can really play around and improve that situation, because you have something to go by.

And once we do this--I think if you really look at this cGMP--the White Paper of cGMP--a lot of these things are already described there in this one. But if you have this formula, you can take it for the manufacturing, and then what you can do, if you are in manufacturing, then you can take some of it and do the evolutionary--EVOP--basically the next slide will show you that one. So you can play around. You can fine tune and improve your manufacturing process. That basically provides some opportunities for continuous improvement and

innovation.

But if you have a product here, you took it for the manufacturing, then really, you cannot change the variables there, you know; anything, any slight change in any variable might change the product, and you don't know where to start.

[Slide.]

So, as I mentioned to you--this is a different example--again from this book--this Box, Hunter and Hunter, 1978, book--basically once you have this optimized formulation, and once you take this formulation, then here, in this case, you have the stirring rate, you have this addition pan--you have the solution pan, you can play around and gradually you can play around. Because you know if you are in manufacturing, you cannot afford to fall outside the specification range. So your window is very, very limited. So if you have a design space, your window--you are well within your window to play around a little bit. So you can gradually work on this and improve the yield. And, finally, you see in the last one, it doesn't improve any

more, you stop.

So this kind of data should be extremely, extremely valuable, extremely useful. And I will provide one or two examples of the laboratory data that we have. I think one of the graduate students had worked on it.

[Slide.]

And I have selected this for two reasons. First of all, it's an extremely complicated preparation; very complex preparation. Here you have a protein, and you are trying to develop a formulation of a protein; a lot of variables in the protein, just to decide on this formulation study itself, we had to do a lot of precharacterization and characterization work. And you will see some back-to-back--two back-to-back papers in J. Pharms this year--February and March, there are two publications--just to decide on the formulation issue that we have to do.

After doing that, then we have decided that, all right, we will try a dosage form--see this salmon calcitonin is a peptide that we have

taken--polypeptide--salmon calcitonin. It was degrading with enzymes. So what we did, we have seen some turkey ovomucoids--a lot of work was already done on turkey ovomucoid--basically it was inhibiting the degradation of salmon calcitonin, the different enzymes--you know; trypsin, the chymo-trypsin, the elastase. It was inhibiting their degradation. So we wanted to use this turkey ovomucoid as one of the excipients to prevent the degradation.

We also wanted to use this glycerotinic acid, because it's protein, big molecule, doesn't go through biological membranes. We have see that glycerotinic acid--we evaluated--we screened almost a hundred compounds. But finally we settled with glycerotinic acid. We have seen that glycerotinic acid enhances the permeation of this protein.

So we wanted to make the dosage form. This is a bi-layered preparation, by the way, and the top layer is very similar to your procardia--you see this dosage form--this bi-layered preparation; procardia, vomax and, you

know, these are osmotically-controlled bi-layer tablets.

So here you have a protein, and then we have this osmotic agent here. If you look at it--so we make this--we compressed this tablet, we made these bi-layer tables. We drill some opening here. We provided some coating to it, so that it releases drug in a particular fashion. It's a dual-controlled release. You have a drug protein--the polypeptide that's releasing, as well as the ovomucoids that's releasing. Extremely complex preparation.

The idea here is: you can see there are so many variables here right now. What should be the coating thickness of this one? What should be the opening of this one? What should be the level of the excipients that you use?

So you can see there's a lot of variability here.

Now, a company that is manufacturing, that's making dosage form, a lot of that information they might have in-house as to, you

know, the coating thickness that is needed; some of the process variables they might already have. And if you don't have it, what you can do, you can actually screen--we have just selected some of them. We have screened some of those variables. We could not do an extensive study--very expensive proteins. We cannot do a lot of experiments. But at least we screened those variables here, at two levels each.

[Slide.]

And then the dependent--the response--the previous one, the example that I gave you--the yield of that compound was the response. But in this particular case, we have the amount released--salmon calcitonin release--in three hours was our response. And then we can also place constraints.

[Slide.]

Now, here, in this case we have placed constraints at different dissolution time points, so you can tailor a release. You can do that. Or you can place constraints on tables. So you're not

interested in a tablet where the hardness is less than 4 KP or more than 8KP. So you can place constraints on hardness, constraints on some of the parameters that you're looking for. So, here, we placed constraints so that we can get the entire release profile on this one.

So by placing constraints, we evaluated that, and we looked at this--the development equation here.

Now, again, as I said, this is just a screening design. You cannot see the interaction effect. The interaction effects are compounded; the quadratic effects are compounded. So a lot of information we are losing, we are missing. But we gathered from here is: of those seven variables that we looked, what are more important, what are less important? Basically we screened those variables.

So if we have to have a few experiments you want to run--so what we did. So we selected out of these three variables, and that we studied at a slightly more detail--I will show you in the

next one.

[Slide.]

We have selected another response design in this time. So basically we have seen the amount of sodium chloride, the osmotic agent that is needed in that particular tablet dosage form, and the amount of coating, and the amount of Polyox--it's the polymer that is required. Basically, these are three variables, and we found that these three variables are more important--at least they're likely to have more effect on the release of salmon calcitonin than other variables.

So we selected these variables. And this was the dependent variable: salmon calcitonin release in three hours--okay? And now we developed this model.

[Slide.]

Now, believe it or not, this one equation can talk more than probably 20 pages of slides, 20 pages of information. Really, it does say a lot.

It says how those variables affect the response. It just shows how X1 changes the

response here; how X2--the coating level--if you increase the coating level, dissolution decreases. I know that. And if you increase or decrease the coating level a little bit, immediately I can calculate the response, without even doing an experiment I can calculate the response. Same thing, I can see the interaction effects of all of them; the quadratic effect.

Basically, by this design sort of experiment, finally we have used a process where we have actually predicted the levels. We predicted that. If you have this much of sodium chloride, this much of coating thickness, and this much of the Polyox levels, then we will get--this is the kind of tailored dissolution profile. We predicted that.

[Slide.]

And what we did, we performed an experiment in triplicate--three, the proof, and then with our product that we obtained was identical to the product that was predicted.

So this is the case study that was done in

our laboratory by one of the graduate students.

I will not go into the details--oh, by the way, this is the response-surface. You have already seen the response-surface for the yield. So here you know at what level you can get the dissolution that you want.

[Slide.]

I will not go into the detail, but, you know, we have also prepared some nanoparticles. We have characterized by a lot of different methods. You can see this publication--International Journal of Pharmaceutics--highlighted all those characterizations. But this one also--these nanoparticles, also--we used a design set of experiments where we have seen, basically, just a formulation variable. We took it at three different variables. After having gone through the screening and all that, we have optimized it.

[Slide.]

And we have seen the dependent variables here. And, again, the observed and the predicted levels were identical in this particular one. It

just shows the levels, as I mentioned to you, about the yield.

And here, if I--after developing this in the laboratory--now, certainly, one has to feel more comfortable taking it to the manufacturing, because they know where they can play around. If you select this particular product here for the manufacturing, you manufacture it, you know you have some room to play around. So you can do this evolutionary operation and play around and improve the product.

[Slide.]

So that is--with this, certain questions that I had for the Advisory Committee.

As I said here, that I'm also learning. I'm also just so new. I just want to orient our programs, or orient our lab in such a way that it reflects some of the agency's thinking, some of the OPS thinking. We want to go in that direction. So you are the experts in this. You have been associated with this for quite some time, and if there's anything that we are not doing you want us

to do, just let us know.

Does a systematic study with a designed set of experiments provide opportunities for reduction of--you know the post-approval, I did not mention it at this time. But, you know--scale-up changes--the post-approval changes--you want to make some tiny change, you keep on getting these post-approval submission documents. If you have some window to play around, certainly, you know, it can reduce. But if you don't agree, just let us know.

Do you agree that the information on design space, with a designed set of experiments will reduce the out-of-spec situations a whole lot more? You know, if you have a very tiny window, any slight change--the speed of the machine, the machine going on and off--just an operator just coughed--you know, or you just change the operator there, or anything might change that situation.

Do you agree that the research with sell-designed set of experiments on lab scale with create opportunities for continuous improvements

and innovations in manufacturing? So industry has got to apply that and provide the data to the reviewer, so that they are not operating under a black box.

So, with this, I think you very much. I'll be happy to take questions. Thank you very much.

CHAIRMAN KIBBE: Any questions for--

DR. SINGPURWALLA: Mansoor, I was told to go easy because you are new. [Laughs.]

[Laughter.]

So I will try and go easy.

DR. KHAN: I can only get something I know.

DR. SINGPURWALLA: The design of experiments--the questions you asked--my answers to all of them is: yes, yes, yes, yes. Because design of experiments is, you know, well recognized and well accepted--particularly by the chemical industry.

The question I have for you is: how do you intend to use design-of-experiments in the

regulatory process? What you have described is the use of design-of-experiments in manufacturing, which is what the industry should be doing. I suspect they are doing it. If they're not doing it--shame on them.

[Laughter.]

But I'm sure they're doing it.

So how do you intend to use this in your particular role as a regulator is what I'm eager to see--or hear?

DR. KHAN: The regulatory questions, I think--you know, some others will answer. You know, it's beyond my understanding at this time.

But my idea here is to provide this understanding to our reviewers; to provide this understanding to our own scientists so they utilize it. And also if we publish more papers--if we just provide this information to others, a lot of others might be more willing to use it.

And as far as the people in the industry using it--you know, some of them are using, some of them are not using. And people might be using it,

but at least they don't provide the information to us at all in any significant way at this time.

CHAIRMAN KIBBE: Okay--

DR. SINGPURWALLA: I see big daddy is coming to defense.

[Laughter.]

CHAIRMAN KIBBE: Go, Ajaz, go.

DR. HUSSAIN: Well, I think design-of-experiments is--what?--a 60-year-old technology that we're introducing. So it's not new at all and so forth.

But at FDA, we don't have the ability to say that somebody has done the work or not done the work and so forth. So we have to assume that what we see is the limited data that companies--many companies do this and they don't share that.

But at the same time, I think surveys done by Professor Shangraw, before he passed--at the University of Maryland and so forth--and more recent surveys, suggested the use of design-of-experiments in pharmaceutical industry is very low. About 7 percent of the companies we

surveyed through the University of Maryland said they actually used design-of-experiment.

So that leads to the concern that we have: if you haven't understood even the critical factors and so forth, how can we allow them to change? So we cannot allow them to change and so forth.

As a result, we have a static manufacturing process.

So, for those companies that do this routinely, that have this sort of information, if this can be summarized as a means to demonstrate what are the critical variables, to what extent the validation ranges can be justified as wide as possible, and so forth--so that provides a means for regulatory flexibility--for those companies that have this type of information and so forth.

For other who do not--not get the benefit of regulatory relief at all. So--

So how would we use this in the regulatory setting? That has been a continued discussion internally. My thinking right now is this is not an FDA policy and so forth. It's--what we would

simply need is to focus on the predictability and reliability of the predictive power that you have developed and so forth. And that should be enough. We don't have to get into deep--there's volumes and volumes and volumes of pages of how was this done and so forth, because our job is to understand what is critical; what ranges are acceptable; and then what is the design space. And how well you know that is through your predictability.

So it's more of a summary type of information I'm looking for.

CHAIRMAN KIBBE: Go ahead, Ken.

DR. MORRIS: Yes, just to follow up--I think part o this falls into the category of having the reviewers understanding the process well enough so that if they do get a good rationale of the formulation and process design, and design-of-experiments that they've really outlined a real variable space, as Mansoor was talking about, that they'll be able to appreciate it.

So part of that is, I think, ensuring, or reassuring the companies that, you know, generating

these sorts of data, they'll receive the proper reception when they get here.

CHAIRMAN KIBBE: Joe? And then I have Melvin.

Go ahead.

DR. MIGLIACCIO: Well, to dispel any myths--yes, we do use design-of-experiments. Aggressively. Aggressively.

I think the issue is is that what we then present is a proven acceptable range; univariant proven acceptable range. That's been the tradition. That's what has been expected.

As we move forward, using design-of-experiments, coupled with the technology we have now to, during those experiments, to monitor the critical variables real-time--we'll move from submitting a static process--a process that is based on a range of time or temperature or any other condition--to a dynamic process that says: "If A, then B." And "if A then B" will be based on rigorous design-of-experiments, with the right multivariate analysis.

So I think that's--you want to respond to that Ajaz? That's--

DR. HUSSAIN: No, I think--we have one similar thinking on that. I mean, ICH Q8, I mean that's the direction I see we're going.

DR. MIGLIACCIO: So it's not going to be a fixed process.

One more--your third question, I have a bit of, I guess--it implies something that I don't think we want to imply: "Do you agree that the information on design space, with a designated set of experiments will reduce the OOS situations?"

You're implying there that you're going to use the design space to set specifications. And that--you know, specifications have to be based on a mechanistic understanding of the formulation and the process, and its impact on product performance--not on the capability of the process.

And the design-of-experiments is helping us to understand what's critical, and what the process capability is. It should not be used to establish finished-product specifications.

And your question there implies--you know, if we set the specifications correctly, and we understand the variability and the measurement system, then yes, good design-of-experiments should reduce--and establishing the design space--should reduce OOS.

But on its own, it won't.

DR. KHAN: I agree.

CHAIRMAN KIBBE: Great.

DR. KOCH: I guess I'll just make a comment that even though the field is 60, 70 years old, in terms of Plackett-Burman and a lot of those studies, it is surprising how little it's used. And you can go into chemical, petrochemical and other industries, and they have not used it very well.

The reason behind it is often the cost of analysis. To do a good study, where you're running a number of variables, you've got a huge amount of samples. And I know, just historically--I got involved in several what they were called "big projects"--that would be eight to 10 variables--and

it was always neck-back, based on perceived cost.

I think, in the future there's going to be a lot more opportunity--addressing your last question--with the development of better lab-based equipment--microreactors, a number of improvements in high throughput designs for other reasons. But I think the equipment's going to become available, and PAT is going to be a vehicle to be able to monitor these things.

And, eventually, I think you'll get down to where you can very effectively use these techniques, often even on continuous processes, where you can invoke feedback and feedforward so you don't have to run a whole number of experiments, but you can be analyzing in real time and adjusting your parameters and filling out your space much more adequately.

But I don't think it's been used very much in industry.

CHAIRMAN KIBBE: Nozer? Ah, we get--you had something else, there, didn't you?

DR. SINGPURWALLA: Yes, I just wanted to

react to Jerry's comment.

I was personally--my prior probability that industry uses design-of-experiments was very high. So I'm not surprised. And, basically, if I was running an industry, I would use design-of-experiments to maximize my own profits and do my business more efficiently.

Industry A and Industry B can produce exactly the same product, but one can do it very efficiently by using design-of-experiments. And the other can do it completely randomly and still come up with the same answer, but you're spending money.

So that was the only comment: that it's more on the manufacturer who has to take advantage of it. And I'm really surprised that they are not using it--based on what I hear from you.

CHAIRMAN KIBBE: Judy?

DR. BOEHLERT: Yes. I mean, I would agree with Jerry: they are using it. There are many companies that are not. And another area where it's used a great deal--particularly the

Plackett-Burman design--is in the optimization of analytical procedures. And I see that in big companies and small companies. They know how to do it. They save their resources and they come up with much better methods in the end.

It doesn't mean that everybody's doing it. So I think to the extent that, you know, folks like you can publish what you're doing, it helps those that don't understand to get on the bandwagon.

But it is used, you know, in industry. It hasn't been overlooked. But not everybody.

CHAIRMAN KIBBE: Anybody else? Comments?

DR. SINGPURWALLA: Well, the only comment I want to make is I studied design-of-experiments as a student. And perhaps it was the most boring subject that I had to go through.

[Laughter.]

It is boring.

[Laughter.]

CHAIRMAN KIBBE: It's always good to have Nozer's opinion on things.

[Laughter.]

CHAIRMAN KIBBE: I think we should more on to Jerry. And thank you very much.

Jerry, your colleagues have managed to leave you three-and-a-half minutes for your 20-minute presentation. And that will allow Vince another 15 for his.

Wrap-up and Integration

DR. COLLINS: This is one person's perspective on the day's events. And for those of you who give talks a lot, it is very difficult to stand up here without any of my props. I have no slides.

I've been scribbling notes all day, since 9:30 this morning, when Ajaz was talking.

One of the most important thins on his third slide was describing the Critical Path essentially as not just another fad at FDA. Some of us are a little shell-shocked by this management agenda, or that initiative and so forth. We have a commitment from the Commissioner--the Acting Commissioner--the Deputy Commissioner for Operations, and our Center Director, that this is

not something that's going away in six months. And to turn the ship around and align it properly, we need that kind of commitment from our leadership, that we won't be thrown into the gulch to do something else later. So, from the perspective of the worker bees, that's very important.

Secondly, several speakers across the board talked about relationships with NIH, going back to the in silico talk from Joe Contrera; both Steve and Amy talked about their relationships with various parts of NIH; and my lab also has cooperation with NIH. I've been at FDA for 17 years, and I spent 11 years at NIH before that. I've never seen a better time for FDA and NIH to collaborate and work together.

There's always been a little bit of "let's make sure we know what our territory is." There's overlap in our interest. There's also things that are uniquely theirs, and things that are uniquely ours. If we just focus on the overlap, I think we really ought to take advantage of, again, what I would call the golden opportunity here for

collaboration.

The other thing that's sort of been missed--I'm surprised there hasn't--maybe I missed it because I didn't get here 'til 9:30--but this week, this month--is really the golden age of quality. I mean, my computer screen didn't have any disk space left a couple weeks ago, after announcements on CMC, GMP, BAC, PAT--I mean, it was just--there have been so many announcements about the importance of manufacturing as an initiative for FDA; about the success of the two-year initiative; the roll-out of the implementation phase. This really is a strong part--a strong era of quality.

I hope it doesn't get lost in the Critical Path. The Critical Path mentions quality issues, but there are so many efficacy and safety issues that we need to be vigilant, and not just rest on our laurels.

In addition to getting your input, we've asked the public for their input. The docket has over a hundred responses. It's all in the public.

You don't--there's nothing secret. If you submit something as a comment--we asked in April--and there's over a hundred--on the website. And if you have a really lot of time--because it's clunky--over the weekend I looked at them all--and it's very interesting. Almost all the comments actually relate to efficacy. There's a few comments that relate to safety, and a very small number that relate to quality. And most of those are actually for biological products of one sort or another; either vaccines, blood-derived proteins, or complex molecules from the OBP domain.

So we need to keep challenging the public so that they recognize the importance of quality. And we also need to look internally, that we're responsive to--you know, our job is to either convince them of the importance of quality, or to re-align our resources.

As I mentioned, in OTR we're about 75-25 chemistry to biology. One of the excuses for having this meeting is so the OTR folks can listen to the OBP folks, and vice versa. And I'm still

learning about OBP. And I get more of a biological flavor each time that I hear your presentations. I don't know that I can fit your round peg into my triangle of safety, efficacy and quality--but that's part of the reason why we're here, so we can learn each other's language, each other's culture, and how it fits.

But I think, certainly, OBP is--actually, the "B" is for "biology"--right? So, you know, you're definitely more aligned with the safety and efficacy side.

What about gaps in our program--various places? Well, first of all, I mean the OTR-OBP gap is really just about finding out about each other. And one of the things that we probably discovered today that would bridge the gap is the Critical Path Initiative--is that all of OPS, and all of CDER, and all of FDA is committed to going down this route. So we all now automatically have something in common, in that our programs must be aligned to the Critical Path.

Now, Steve, I can't do that polygon stuff

that you borrowed from Ajaz, but in terms of a bridge, I can think of the Critical Path Initiative as something that connects two pieces.

The other thing is that product quality is important--as everybody in this room thinks it is; needs bridges to the clinical side, to the pharm tox side, and to the clin pharm side. And so when Ajaz talks about the ICH Q8 principles as one of the ways that we can actually bridge these things, this is really important. We can't do product quality in isolation. And a hand-off from one to the other has been covered in several of the talks. But that's an area where we need to focus: on making sure there isn't a gap there.

The other thing, in terms of keeping reviewers and researchers together--we have two distinct models that have been discussed here this morning. John Simmons made a number of comments bout the way Office of New Drug Chemistry interacts with Division of Pharmaceutical Analysis, and Division of Product Quality Research. Lawrence Yu mentioned several projects that they've been

working on there. And then--and the OBP side, we have the reviewer-researcher model that both Amy and Steve articulated in their talks.

Those are somewhat different approaches. In CDER, we have tried the reviewer-researcher model, with very minor success. We found that geography is a terrible burden and barrier--not to mention use-fee deadlines and growing workloads on the review side. So people who initially could do both research and review eventually had their desks swallowed up with all kinds of electronic copies of documents, and found it hard to continue.

For the last 10 months OTR--a large part of us--have been out at White Oak. And starting in April, the immediate office of OPS--including the in silico group--the Office of New Drug Chemistry will all be there in the adjacent building. And there is a physical bridge. It's just not a conceptual bridge. The second floor of our laboratory building is connected to the second floor of their building. I think that will facilitate reviewer-researcher models, because it's

location, location and location.

Now, it's not the whole thing. I mean, the Office of Biotech Products is still on the NIH campus for the foreseeable future. And our laboratory in St. Louis is there for the foreseeable future. So we don't have a fully-integrated geographical solution to our gap analysis, but it will be an interesting experiment to see, particularly, how ONDC and the first floor of the lab building interact, and whether that improves the situation.

Last comment is that we're supposed to be "science-oriented" here. And although the Critical Path in drug development is a fact, it's well-documented, it's only a hypothesis that we can do anything about improving it.

We've laid out today--throughout the day--a number of approaches that we've been thinking about implementing, and have started implementing, but it's only a hypothesis that they'll work. The chances that they will work are enhanced greatly by getting feedback from talented

people--from the public, from the industry, from the Advisory Committee--taking that advice to heart, and really giving it its best shot. Any initiative fails if it's only a half-hearted initiative, or if it's not well designed, or if we don't have the right equations, or if we're 60 years behind in the technology. So--we appreciate any forward-thinking ideas you may have in that regard.

CHAIRMAN KIBBE: Okay.

Ajaz, help me here a little bit. Would it be best for us to go ahead and let Vince do his presentation and then take the three questions you have sitting around here?

DR. HUSSAIN: Right--I mean, Helen and Keith and I were just discussing that, in a sense, because we have received constant feedback from you throughout.

CHAIRMAN KIBBE: Right.

DR. HUSSAIN: Maybe after Vince's talk you could just summarize, instead of getting into answering all the questions in detail. But I

think, since we have received so much feedback, if you could just summarize the Committee's thoughts, it will be fine.

CHAIRMAN KIBBE: That means you're up, Vince.

Challenges and Implications

DR. LEE: Okay, great. Maybe I can start with the questions.

[Laughter.]

How am I going to work this thing?

[Laughter.]

Thank you.

Okay--thank you, Ajaz, and also thank you Helen and Ajaz for giving this opportunity to work at the FDA. It's an eye-opening experience, and I recommend it to everybody. Because you get a different perspective.

I was changing my talk as I was going along, and that's why I was away for the first hour of this afternoon; I didn't not that I would have to make another copy that corresponds to my slides. So that's something that also I learned.

Let me be more precise about what do I see as the implications and challenges.

[Slide.]

The one thing is always to increase the return on investment by fostering an innovation. "Innovation" is the key word. And also, along the way, we hope to improve the quality of life for the patients, and lower the costs--the health care costs--for society. In fact, as I was sitting around the room, I wish that maybe sometime down the road that we should include economists in the committee to give us some assessments.

I wanted to look forward and see if we were to follow this Critical Path Initiative, what is the benchmark. What do we expect to see?

[Slide.]

And I'm trying to be cooperative, because I have no clue about what should we expect. And I don't know whether we can assume one number, because each drug is different. But let's say that maybe in five years' time--by 2010--then let's commit to lower the development costs by 30

percent, shorten the development time by 50 percent, and increase success rates by a factor of three. I have no idea if this is realistic or not, but maybe we should start thinking about that.

And what else might happen? I would expect that more drugs will be launched in a controlled delivery platform when our sustained-release system is used as a line extension. So I'm proposing that his model will be different.

Here comes the next point, is that the sponsors of compounds might be forming a consortium to share information and knowledge. This is something that's not being done today. Obviously it's because the conditions don't encourage that. But we're in different times. And so maybe perhaps we should think about different models.

And, moreover, maybe the sponsors will subject their science to peer review for open access in the global community. I would home that maybe sometime down the road that equivalence, or the genome project, would be reproduced in the drug

development arena. Now, this is something which is quite naive, you might say. But I just want to put it out there and see who would challenge that. And I would be a bit worry that one reviewer, to make judgment on one product--part time editor at the same time.

[Slide.]

What else might be happening? Well, the era of blockbuster might be over. I don't think at this point in time few executives would believe in it. And, frankly, I do not know how the agency can confront this avalanche of applications if everybody's looking at just specialized populations. But I do think that a new era would arrive where we'll be more realistic to look at narrower indications, and then use the patients--the users--to expand the knowledge base. And I'm proposing that perhaps all of us would be enticed to participate in a Phase IV study by using the chips which are recently approved by the FDA. This is subject of another big talk.

And then there will be a growing of

nano-sized assemblies with specialized functionalities. Now this is something--I'm not that fascinated by nanosystems. What intrigues me about nanosystems is the capability, for the first time, for the device circulating in our body, collecting information, providing feedback to the scientists. So I envision that maybe we can look at nanosystems as satellites. This is something that the body has never been exposed to. I have no idea how the body would respond to it. But intriguing to find out. Again, that would the subject of another long presentation, talking about diseases for which we need a way to assess the early change. Cancer is very dreadful because by the time we see the symptoms it's already too late. Would it be possible to have a micro-chip circulating in the blood stream, collecting information that would report the scenario--fingerprints characteristic of disease--and that information would be fed into a computer, and a database on that basis, a diagnosis would be made.

So what I'm proposing is that maybe we're approaching an era of preventive medicine, where the patient would be at the center of the whole process.

I'm going to just give a few slides in the interest of time.

[Slide.]

This is a very intriguing slide to me, because the reach limiting step--we talked about changes, depending on the time. And depending on the thinking of science at that time. 10 years ago, in 1991, PK was a major problem. Now everybody was focusing on PK, and now something else popped up, a formulation, which was not a major problem in 1991, becomes a major problem. Who knows what it's going to be?

So what's the message? The message is that we have to be always in touch with the leading edge of science, and where the leading edge resides is in the sponsors.

So what are the implications? The implications are in four areas, as I see it.

[Slide.]

In terms of individuals, I think as scientists that we can no longer focus on just one thing that we're looking at. We have to have a 360 degree vision. And this is along the lines of what Ajaz talked about--having a common vocabulary. I don't know his name--but he's gone.

So the next point is the infrastructure. How can we organize the scientists in such a way they can respond to new opportunities on short notice? I understand there's a SWAT team already in place, but we need to have more of these in the agency.

There have to be incentives, in terms of incentives to reward innovation and teamwork. Again, it's different times.

And finally, I see there should be some kind of interrelationships--with the NIH--I agree with Jerry, I think this is a golden opportunity for NIH and FDA both being part of the HHS to collaborate, to reinforce one another. I think this is--and also, I think that the move to White

Oaks is very symbolic in the sense that for the first time the agency's under one roof.

So I think that, whereas in the past nobody talked to anybody, it's time for us to work together, to exchange information. And certainly I think the agency might consider sponsoring projects.

[Slide.]

So what's next? I think that we need case studies. This is easier said than done, but I think there's a lot of information--data--in the FDA archives. I don't where it is. I don't want to volunteer to go look for it. [Laughs.] But I think somehow we need the information, and demonstrate that--under what conditions we can categorize drugs in the same way as we do at the BCS. And I think we need some kind of organization to organize our thoughts.

We need some benchmarks, what should we be looking for, if the Critical Path Initiative were to succeed. I think it has succeeded.

Now, which sectors would apply this road

map to? Well, it was designed for big PhRMA. But what about generics, biotechs and start-ups? And who else? So we need to think about that.

And, finally, which drug class should we begin with? And here we have no definitive answer. But this is again a very interesting summary in the nature of drug discovery, where it says that the success--the percent of success--depends on drug class--for obvious reasons. And I think that we need to look at information such as this and do a quick demonstration project to convince the skeptics that it is the Critical Path concept is viable.

[Slide.]

So what are the challenges to all this? I think this is a recapitulation of what was said throughout the day--communication. I think everybody should understand what is meant by Critical Path. And we should all follow the same Critical Path. You go different Critical Path, I think that we go nowhere. So broad understanding and shared goal community-wide is important.

I think we should have a mechanism to inspire the leaders among the scientists to create new paradigms; and also to motivate the scientists to adopt a new approach to decision making--willingness to learn, and to unlearn, to relearn--and learn. This is something that I'm trying to do myself.

[Slide.]

This is Ajaz's favorite: the knowledge management. When he first talked to me--not 11 months ago, but six months ago--I had no clue what he was talking about. But finally I saw the light.

And we're definitely living in the knowledge era--and there's no question about that. And there was 200 years difference--200 years' span between the industrial era and the knowledge era. And the characteristic of the knowledge era is very different from the industrial era. Where, in the past we focused on single entities, now we're going to have the ensembles. And why is that? That's because in the past, we had no access to organizing information; that we tend to think--we reduced

everything to a single entity. This may be the physical chemistry influence on the formulation.

But when you find in the real world that usually--not only single entity, but the things work together as a team, an ensemble.

In terms of scientists, they no longer can function as an individual; I mean, accomplish everything individually, but has to have a network. The success of science depends on the network of all our colleagues.

Things are moving very fast in the knowledge area. And things are dynamic. And I think that we always are in view of sharing information--sharing knowledge--whereas, in the past, rewarded by being proprietary. Now this is something which is very challenging, in my opinion, to convince. Everybody think differently--because we never know what the outcome will be. But at the present time by protecting information, then we move forward. But as a scientist, myself, I'm always troubled by the duplication of efforts. Oftentimes, you know, it's the failures that will

be useful, because at least I know that I will not go down the same path.

And then it's very clear to me that--the thing about my children, when they come along to use this benefit of medicine in a major way, it's definitely in a consumer-centered society, where the consumers will know about health. And hopefully, I think our government would promote health education in the public.

[Slide.]

So what is the road map? It's very simple--three things.

One is that we need to provide incentives for industry and academia to formulate and test alternative drug development schemes. And there's no reason why drugs should fail in Phase III. If they fail in Phase III, there must be a reason. They must not be doing something right.

The second thing is that we need to think about coordinating data mining worldwide for forecasting hurdles to drug action, delivery, formulation and manufacture. We can learn a great

deal from existing information.

And the third think was talked about, again early this morning--is the computational tools. I think that if we have access to simulation models we can begin to test the weak points--the critical parameters--and design experiments properly, then we might be able to do clinical studies more efficiently.

So this is the three things.

[Slide.]

So what are the--the three last points I would like to leave with--the three areas--one is outreach. I think that we definitely should sponsor retrospective studies on the value of sharing knowledge in accelerating drug development and rendering it more precise. I think that we can--although the past is no prediction of the future, but at least we know what is the scientific foundation.

The second proposal I have is to think about convening a summit with industrial and academic scientific leaders to identify the pros

and cons of what I proposed in the first, and to understand the mechanisms to conduct data mining without putting the innovator at a competitive disadvantage. So I'm proposing we should think about a strategic plan for drug development. This is very far-fetched, but I think we should contemplate this framework.

The second area that we should focus on is the process. And, again, summarizing what was talked about all day today--to examine. the current review practices with respect to fostering innovation and then propose necessary changes. And the second point I would like to propose to be looked at is to develop mechanisms for facilitating continuous improvement in the quality of approved products. I'm talking about the generics in this particular point. There may be about eight years' span between the launch of the innovator, and the launch of the generic products. But science has improved a great deal. Have we learned from it? And how can we take advantage of these advances in science.

And the third point is to be proactive in identifying cutting-edge research of pharmaceutical relevance that would fuel innovation. So, clearly, the whole points of Critical Path Initiative is to encourage innovation.

The last point is human resource. I think it's something that, as a former academician, education is of great value. And in fact, my former university has a regulatory science program. I don't think it's appropriate for the future. And I dare to say that in front of my former dean. And I think that we should do something differently, because we should prepare the regulatory scientists of the future.

In fact, I think it's very important for us to think about the scientists on line five years from now, and what do we need five years from now. So I think the education of the regulatory science programs--most of the programs in the U.S.--perpetuates what we have today. So we need to think differently.

And then the second point is a point

addressed to the agency, is the current practice of recruiting scientists and retaining them, as far as development of leaders from among the ranks. I think this is central, and I do believe that science has to drive the process, and research is an essential component, and there's a lot to be learned from the OBP part--the CBER--whether you have research--where there's the opportunity for research.

But the research that we do has to be different--unique. And there's an unmet need. And clearly it would be the bridge between academia and industry research.

So--these are my thoughts. And certainly if there's an interest, I will answer easy questions.

[Laughter.]

Committee Discussion and Recommendations

CHAIRMAN KIBBE: I don't have easy questions. I think you've said some very interesting and thought-provoking things.

I've been thinking about everything that's

been going on today, and I know Ajaz suggested that we might come up with some kind of a summary for the questions today. And I really don't have a good summary, but I have a lot more questions.

And what I think might be useful is those of us who are staying for tomorrow to spend the evening thinking about all of the things that we've heard, and how it all comes together.

The human mind--as opposed to the artificial intelligence that sits on our desks--works in patterns and pattern recognition, instead of sequences of computational paradigms.

But a couple of things come to mind that I'd like to share with you, and then maybe we can--I'll let you gentlemen ask questions if you have any.

DR. LEE: Maybe I can add two points. One point I should mention is, as a former chair of this committee, that what--how could the committee be more--let's see, I don't want to use the word "useful," but since it's on the tip of my tongue, I'll just say it--more of an asset to the office.

And this is something that I think I would be interested to hear from this group, about how the committee--how should the committee function to--you know, in the Critical Path Initiative. So that's one thing.

The second is that I think sharing information is critical. And the way that things work now is that information is passed from one module to the next. I think that's in today's world, the way that the human works is to multitask. So any time information is available to all the stakeholders in the enterprise.

CHAIRMAN KIBBE: Let me continue with some thoughts. First, the question of the Critical Path Initiative. Are we focusing on the appropriate Critical Path?

The question I have is: is the output, in terms of new and novel chemical drugs a result of something that we need to work on in order to prove the flow-through, or is it the result of a paradigm that was begun early in the 20th century and has run its usefulness? Are we actually at that asymptotic

curve where we spend tremendous amounts of energy to get a small breakthrough, but unless we have a significant paradigm shift we're not going to get there.

Are we asking ourselves that we new drug entities? Wouldn't we be better off asking ourselves that we need new and better therapeutic ways of treating disease or preventing disease?

And maybe the shift that we went through, away from surgeries and manipulations, to the use of chemicals in the last century is over, and we need to go into a different therapeutic thinking. And if we can't make that paradigm shift, applying tremendous amounts of energy to an old paradigm that's running out of steam, isn't the way to get there.

There's a lot of interesting new technology on the horizon: computational power, and what Vine talked about--which some people call nanobots, are coming. And in 10 to 15 years we will be at what some have characterized at a singularity in our understanding of computational

power; a day when the ability of a desktop computer to think in patterns and reason--as well in patterns as it does in digital format--will allow it to acquire data off the internet and come up with answers we haven't even asked the questions for.

And are we right now at that juxtaposition where our traditional way of going about looking for new therapeutic moieties is running into the wall.

DR. LEE: Well, I think that we are, because I think we leave the treatment with a single compound may be on the way out. And more likely that we are beginning to treat diseases with combinations. Usually when disease, more than one thing goes wrong.

Also, I too believe that with the day come where you can hand in an application, then computer will look at it and say, you know, yes or no. It might--because, you know about is the pattern recognition.

DR. MEYER: Yes, a couple of comments.

The agency loves acronym's, as we've seen today. And I think it's interesting that "Critical Path Initiative" is the same as "Consumer Price Index."

[Laughter.]

They are related. We're trying to save money, get things out sooner, make people weller. So that's interesting.

Jerry used the term "hypothesis." And I didn't hear what the hypothesis was necessarily for all the things we've been talking about. And then Vine, on page 5 said, "benchmarking." And I think--well, he made up some--50 percent this, and 30 percent that in 2010--I think that would be worthwhile, to show people where you intend to go.

Just a couple of comments that really deal with the questions: prioritization in the era of limited resources. Obviously, you have limited resources. I think there's an impressive quantity of work that was presented today. It was much like going to an AAPS symposium. It was just high-quality stuff.

And certainly I was brought up to learn you'll be a more effective teacher if you're involved in research--much like you'll be a more effective reviewer if you're involved in research. That was kind of my fair-and-balanced part. That was the fair part. Now let's get to balanced part, if I were a Senator on the Budget Committee.

We all know FDA has difficulty--a difficult time with criticism about speeding up approvals; difficult time with recalls of marketed products; difficult time with a shortage of OGD personnel--and a litany of other things.

So, given that era, I think it's going to be critical to prioritize what you're doing in terms of the Critical Path Initiative or any of the other initiatives.

And let me just pose a couple of questions that I would ask if you were telling me what your priorities were: who else could do the work? Could NIH? Could industry? Could academia? Could CRADAs solve the problem? Who else could do the research? Who else should do the research? Are

there really other groups that are better able to do the work, rather than you re-inventing a laboratory, and a process and equipment and personnel etcetera? Are there other people that should do it?

How can another resource outside the FDA be encouraged--with a carrot--or forced--with a stick--to undertake some of the things you're already doing? I would use an example: you publish a guidance, and before long there's all kinds of people that are willing to train--for money--industry; all kinds of people that are welling to development instrumentation to help industry. So you put an idea out there: "Henceforth, in 2005, we will require that," somebody's going to figure out how to do it with some piece of equipment, and market it, and that will be good for the whole economy, and you won't have to do it.

I would ask how does the research relate to problems faced by FDA--not globally but, you know, right now you have conjugated estrogens.

That's an issue. I don't know really who might do that work. And then what is the importance of the problem?

So I'd say: are there others capable of doing the work? And what is the importance of the problem? And how does the problem relate to something closely involved with FDA.

CHAIRMAN KIBBE: Ajaz, what do you think? Shall we farm it out? Outsource it?

DR. HUSSAIN: these are very, very important questions. And I think the benchmarking--the hypothesis--clearly, anything that we do, unless we have a goal in mind, unless we have a plan in mind, we're not going to get there. And that's the reason the overreaching OPS immediate office proposal we said was we will go through some of the process, trying to map this out, define the metrics and so forth. That would be essential.

And clearly, I think, an initiative umbrella creates expectations, creates a benchmark that I think people will hold us to and so forth,

because nothing is free in life. So any funding--anything that we get to support these activities--will have an associated accountability and efficiency in metrics.

So I think those are very important questions that I think we will have to sort of build into our thinking as we move forward.

CHAIRMAN KIBBE: Ken?

DR. MORRIS: Yes, just to follow up on a couple points.

First, I think--to your point, Art--that in the future I think therapies are going to be a lot different; and, hopefully, significantly different. But in the interim, between now and then--given our 401(k)s and all--the thing that strikes me most in your presentation Vince--other than the eloquence, of course--is the Nature Review's drug discovery article, and particularly the attrition for each criterion, versus the criteria.

And if you look at those from the '91 to 2000, what you see is that, in fact, tox has

certainly gone up significantly, but cost of goods has gone from zero to 10 percent. Formulation has gone from zero to 5 percent. Commercial -"commercialization," I'm assuming--has gone from 5 to 22 percent.

So I think those statistics really are pretty much in line with a lot of what the 21st Century GMP initiatives, as well as the Critical Path Initiatives were pointing out. I think, overall, this is telling us that those are the areas of opportunity.

The statistic you used about, you know, decreasing the cost part by 30 percent is really very consistent with what G.K. presented at the manufacturing subcommittee last time where, if you'd look at the current cost of goods sold as 25 or 26 percent of the current burden--if you can reduce that by a third--say 30 percent--and apply that to the discovery R&D--as long as we're still in the paradigm of traditional chemical discovery--that you can increase the discovery budget by 50 percent.

DR. LEE: Oh, that's true. Yes.

DR. MORRIS: So that I think your benchmarking is actually pretty--I mean, you know, if not realistic--if it's not realistic we're in trouble. I think it has to be realistic. I think those are the goals we have to shoot for in the short term, all the while keeping our eye on the ball of the new therapies, I think.

DR. LEE: Your on the same lines that we shift the responsibilities to--well, the upkeep--the maintenance of the quality to the manufacturers. So I would see that there might be a reduction in the size of the regulatory program--departments--and more resources that can go into research.

CHAIRMAN KIBBE: I guess we're getting--we're running out of time, and I think we probably have--do you have something, Jurgen?

DR. VENITZ: [Off mike.]I always have something.

[Laughter.]

CHAIRMAN KIBBE: I mean, do you want to

say something.

DR. VENITZ: [Off mike.] A question we wanted to acknowledge or--

CHAIRMAN KIBBE: I don't know. Turn on your mike.

DR. VENITZ: Two comments, then.

One has to do with the fact that I'm concerned that we're trying to overreach. I mean, FDA has only but so much impact on attrition rates, on drug development. And I think the major part of--not drug development, but the discovery part, you have no control over. And you shouldn't have any control over.

And my reading of those numbers that we've seen, if I look at efficacy--30 percent fail efficacy now, and they failed 10 years ago. Well, maybe the wrong target was picked. Maybe we don't know what the target does. Maybe we don't know how the target is related to disease. That has nothing to do with regulatory science. That has nothing to do with product quality.

So I do think we have to kind of step back

a little bit and realize there's only so much of an impact--no matter what your goals are, no matter whether you reach them or not--that you can have an impact.

The second one--and that's one that you've heard me talk about for whatever--however many years I've been on this committee--and that is to really embrace this concept of risk; that risk is something that is intrinsic to being alive. Being alive is a risk because we're all going to die. So the question then becomes: how can we quantify risk? And how can we link that to--in your case--product performance? And that, to me, is really essential.

So all the rules that you come up with cannot be driven by the ability to measure certain things; certain what you consider to be critical attributes. But they have to be really driven by the fact that we think there is a reasonable link between improving those attributes and some risk to the patient; and that the stakes are high enough for us to put all the resources in, in terms of

controlling that risk.

So--two comments; one, that there's going to be a limited impact of whatever the Critical Path Initiative that the FDA proposes will do; secondly, that you really have to emplace this concept of risk, and feed that back into your critical attributes, and the whole cGMP change.

CHAIRMAN KIBBE: Ajaz has a comment.

DR. HUSSAIN: I think the discussion is sort of coming together, in terms of giving us very valuable insight in sort of the questions that we need to pose.

If I may impose on the committee to--as the Chair suggested--take the evening to think about these.

But what I would sort of build on Marv's and Jerry's presentation, and Vince's, is: I think the key is the metrics, in the sense, I do believe in this, since we don't want to overreach; we need to understand where our impacts will be the most positive, as Jurgen just sort of pointed out. And we need to have some meaningful metrics to measure

whatever path we decide to walk on, and measure our progress in that direction.

So if the committee members could think about--from that--the discussion perspective now, to sort of come back tomorrow to sort of summarize some of their thoughts on some guidance on how we should move forward here, it would be very useful.

For example, I think just building on Jurgen's comments here, in the sense: where can FDA have the maximum impact? And how can we measure that? For example, I think--I look at this slide here, and I say all right. Traditionally, formulation was never an issue. Why is it showing up as an issue now? Are the drugs more complex that we're not able to--the product itself is so complex? Or--so there are some indicators here which were surprising, and so forth.

So if FDA has to have maximum impact, how will we measure it? Multiple review cycles is one measurement that we can look at.

For inhalation products, we have multiple review cycles. If I look at our root-cause

analysis, the physical characteristics is a CMC which leads to multiple review cycles as soon as you have a drug and a device combination--inhalation product. We cannot even approve a generic product when it's inhalation because of that level of complexity.

So--multiple review cycles, and reduction of that could be a metric. I'm just asking you to think about it.

Approval decisions--I think, with respect to the example of PET imaging, how some of these things impacted on approval decisions could be an aspect that we could measure.

Clearly, I think, as we move towards follow-on proteins, expand the generic programs and so forth, within OPS we have a Congressional mandated committee that we manage, which is a very difficult task. It's the Therapeutic Inequivalence. We don't have a good means to manage that--reports that come in--because our information is limited.

Keeping an eye on post approval reports

that come up--is that a means to measure that? I don't know.

So I think if the committee members could think about the discussion here, what metrics, how can we measure this, and then come back with their thoughts tomorrow, that will be wonderful.

DR. LEE: May I interject, also, I would like to plead for the funding in the formulation area. I think that was talked about this morning. There's no department on pharmaceutical technologies. And I think somebody should make the case to support formulation in a big way.

CHAIRMAN KIBBE: Marv?

DR. MEYER: Just one suggestion--kind of passing the buck, I guess--it seems to me it's a little more efficient if some representatives of FDA threw up a straw man tomorrow morning, because they know what the problems are. They know what potential solutions are. They've come up with the Critical Path Initiative--throw up a straw man, maybe with a couple examples, and let us hack at that, rather than have us kind of out in a blind

somewhere try to come up with some harebrained ideas that will be in the public record.

CHAIRMAN KIBBE: I plan on doing that tomorrow, though. That was my whole thing with tomorrow.

It would be nice to hear from our industry reps, too. Because they have to live with the challenge of finding better ways, and more efficient ways of improving the quality of the therapeutic moieties on the market, and doing it in a constricted economic environment.

DR. MORRIS: Just to follow up--one think I was thinking is that in some of the work we've been doing with Ajaz's folks, and Helen's, we've been looking at the CMC review process. And maybe some of what we've been doing could be classified as dividing it into opportunities for improving the reviewing efficiency, versus real scientific changes that have to be made to stimulate the process--which I think sort of is reflected in this slide here.

CHAIRMAN KIBBE: I think it's time to call

it a day.

You can turn off the tape, and then I can say really weird things.

[Whereupon, the meeting was adjourned, to reconvene on October 20, 2004.]

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