FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MANUFACTURING SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

8:30 a.m.

Wednesday, May 21, 2003

Ballroom Salons A-D
Gaithersburg Marriott - Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, Maryland 20878

ATTENDEES

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ATTENDEES (Continued)

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FOOD AND DRUG ADMINISTRATION STAFF:

JOSEPH FAMULARE
DAVID HOROWITZ
AJAZ HUSSAIN, PH.D.
HELEN WINKLE

ALSO PRESENT:

COLIN R. GARDNER, PH.D.
Transform Pharmaceuticals Inc.

C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

DR. BOEHLERT: Good morning. My name is Judy Boehlert, and I'm chairing this Subcommittee on Manufacturing of the Advisory Committee for Pharmaceutical Science. I always have to stop. I always say it the wrong way. I say Pharmaceutical Science Advisory Committee.

I welcome you all to today's meeting and tomorrow, hopefully, as well. I'm looking forward to a very productive interchange of ideas. I know we should have that based on the caliber of the committee members I see here, and I'm looking forward to your input.

Our first order of business this morning is to introduce ourselves for the benefit of those on the committee who might not know everybody and for those in the audience. As I said, I'm Judy Boehlert. I am a consultant to the pharmaceutical industry and I consult in areas of quality, regulatory affairs, product development on scientific and compliance issues.

So if we could start around the table, and Efraim, if you would introduce yourself. It's a way to check if the mikes are working as well.

DR. SHEK: Efraim Shek from Abbott Laboratories.

DR. LAYLOFF: Tom Layloff. I'm with Management

Sciences for Health, an NGO working developing health systems in less-developed countries.

DR. SINGPURWALLA: I'm Nozer Singpurwalla, George Washington University.

DR. PECK: Garnet Peck, Professor of Industrial Pharmacy, Purdue University.

DR. HOLLENBECK: I am Gary Hollenbeck, Professor of Pharmaceutical Sciences at the University of Maryland.

DR. DeLUCA: Pat DeLuca, Professor of Pharmaceutical Sciences at the University of Kentucky.

DR. TEMPLETON-SOMERS: Karen Templeton-Somers, acting Executive Secretary to the subcommittee.

MR. PHILLIPS: Joe Phillips, regulatory affairs advisor to the International Society of Pharmaceutical Engineering.

MR. SERAFIN: Dick Serafin, consultant primarily in the manufacturing area.

DR. GOLD: I'm Dan Gold. I'm a consultant from D.H. Gold Associates. We consult with regulatory and manufacturing compliance issues.

MS. WINKLE: I'm Helen Winkle. I'm the Director of the Office of Pharmaceutical Science, Center for Devices -- Devices.

(Laughter.)

MS. WINKLE: Boy, I'm not too quick this morning. Thank you. I've been on vacation for a couple of days. I forgot where I work. Center for Drugs and Evaluation.

DR. HUSSAIN: Ajaz Hussain, Office of Pharmaceutical Science, CDER.

DR. BOEHLERT: Thank you.

Our next order of business is Karen Templeton-Somers will read the conflict of interest statement.

DR. TEMPLETON-SOMERS: 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 at this meeting.

The topics of this meeting are issues of broad applicability. 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. Because they have reported interests in pharmaceutical companies, the Food and Drug Administration has granted general matters waivers to the following SGEs which permits them to participate in these

discussions: Dr. Judy Boehlert, Dr. Patrick DeLuca, Dr. Daniel H. Gold, Dr. R. Gary Hollenbeck, Dr. Thomas Layloff, Dr. Thomas Peck, Dr. Gokeju Raju, and Mr. Richard Serafin.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, Mr. Joseph Phillips and Dr. Nozer Singpurwalla do not require general matters waivers because they do not have any personal or imputed financial interests in any pharmaceutical firms.

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member and consultant.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited guests, Ken Lavin has no financial interest or professional relationship with any pharmaceutical company. Gerry Migliaccio is employed full-time by Pfizer, Incorporated, and is a member of PhRMA GMP Steering Committee. Glenn Wright reports he is employed full-time by Eli Lilly & Company.

We would also like to disclose that Dr. Efraim

Shek is participating in this meeting as an acting industry representative, acting on behalf of regulated industry. Dr. Shek reports that he is employed full-time as Divisional Vice President for Abbott Labs.

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 product they may wish to comment upon.

I would like to back up a little. I think there was a typo here. It's Dr. Garnet Peck. Right? Not Dr. Thomas Peck. Okay, thank you. And he has a general matters waiver.

DR. BOEHLERT: Thank you, Karen.

Our first speaker this morning is Helen Winkle, and she will introduce the topic in today's agenda.

MS. WINKLE: Well, my job this morning is to welcome everyone here on the Manufacturing Subcommittee. It is really nice that we could get together. The last time we were scheduled to meet, which was the first meeting, we had an orange alert. The war was starting, so

we had to cancel the meeting or postpone the meeting, and here you all come today and we have another orange alert. So maybe it's the subcommittee.

(Laughter.)

MS. WINKLE: But anyway, I want to welcome everybody.

This is a really exciting time for us in OPS. We're really excited about getting this subcommittee started. I think there are going to be a number of really important issues that are going to come before the group, and we are looking forward to working closely with you on those issues.

I just want to give you a little idea of why we're having the Manufacturing Subcommittee, where it sits in the structure of the Advisory Committee for Pharmaceutical Science, and just an idea of what we anticipate that this subcommittee will do.

Why was the committee established? I think mainly what we were thinking about from the advisory committee standpoint was it was important for us to focus on manufacturing science. It's a real important part of what we do in the Office of Pharmaceutical Science and a real important part of where we're going under the GMP initiative. It affects not only how we do review, but how we do inspection as well. We felt like it would be very

helpful to have experts from outside of the agency to work with us so that we could get a better understanding about manufacturing and a better understanding of where we needed to go with our various initiatives.

Basically it's a time to look at what is critical for quality and design in manufacturing. It's really important that the whole agency focus on this, but again, we need some help in looking at what is critical to quality and how we need to go about doing this.

Also, we think it's important that we be open in our communication on this, and through the subcommittee, it is an open public meeting, and there are issues I think that we can talk about publicly here that will help all of us, both in the agency and in industry as well as others, to help understand what we're doing and where we're going and also focus on what we hope to accomplish over the next few years with this subcommittee. I think we're going to look at levels of information and data that are needed in the applications in the review side, and we'll also look at changes to manufacturing and, through the committee, help us understand better what we need to be focused on when we're looking at these changes.

One of the examples of that is comparability protocols. We already have a draft out on comparability protocols. But I think many of you might have been at the

GMP workshop a couple of weeks ago. There are still a lot of questions out there that need to be answered both from an agency standpoint, as well as the firms' standpoint. So this will give us an opportunity to take a look at things from the subcommittee and to get some assistance from the subcommittee on where we need to be going.

We need to validate the science behind the review. I think this is very important to all of us in the center. I think there's a lot of science in the review area, but I think that we need to have a better handle on that science and better focus on what it is.

Also, I think the subcommittee can help us address the science that really needs to be validated through research. We have the capabilities of doing that research internally, as well as through our Product Quality Research Institute. So I think the subcommittee can be important to us in thinking about those areas where we need more data, we need more information, and helping us to focus on that.

Basically why now? Why have a subcommittee now for this? I think, first of all, the time is right. We need to look at change as being good. There is a lot of good change out there, and I think the agency has been hesitant to move toward change. We in the agency now realize that we need to do that. We need to change

internally, as well as work with industry, to begin to implement change, and we need in the agency to be able to facilitate that change.

And by facilitating that change, I mean understand what is needed, what we need as far as good manufacturing science, what we need as far as good quality built into the design of the products, and we need to have a better understanding of that. We hope to work with every one of the members on the subcommittee to help us think through these changes, to think through what's needed, and to help in facilitating that and what we need to do to facilitate that.

Also, we need to focus on risk management. I think that every place you go now, there's a lot of talk about what's risk management. In some cases, we're not completely certain what are the elements of risk management. So working with the subcommittee, we hope to be able to have a better handle on that. At the next meeting of the subcommittee, in what we hope will be October, we really want to look at some of the risks that are out there and how best to prioritize those when we're looking at taking compliance actions or doing some inspections in the future.

Of course, I've already mentioned the PAT initiative and the GMP initiative. These are two really

important initiatives in the center that have been driving us forward for the last almost year-and-a-half/two years, and they are very important to what the subcommittee will be doing. It's a good time to bring the subcommittee together to sort of help facilitate both of these initiatives.

There was a PAT Subcommittee. I think there were several people here on the subcommittee that are on the Manufacturing Subcommittee. There are still areas that we need to pursue, and I'm hoping that the subcommittee can do that.

I mentioned the GMP workshop. There were a lot of issues that came up, a lot of questions that came up at the GMP workshop. A number of these questions still need to be answered internally in the agency. So we're hoping, with the help of the subcommittee, that we can answer some of these questions and begin to put out information and data that will be helpful to industry.

The CDER/CBER merger. There are new therapeutic products, of course, that will be coming under CDER's jurisdiction, and we need to take a look at what best principles are. I think we'll have questions along the line. We really will see a number of elements in both areas, in the CDER products and in the products that are coming over from CBER where we need to answer questions on

how best to address review issues with those products. So I think the subcommittee can be very helpful here, and it's very timely the subcommittee is being set up at this time.

Of course, global harmonization continues to be an important part.

And lastly, I have on here better resource utilization. This is important. It's important to us in the center and I know it's important to all of you in the firms, and I hope to work closely with the subcommittee as we think about how best to utilize our resources, especially in the center as we move forward in the 21st century.

The other thing that's important too is we find more and more need to coordinate between some of the issues that we have with generic products, as well as new drug products. There are things that will come up at this subcommittee that will affect both areas of regulation and areas that we need to answer questions on how best to address. So, again, the time is ripe for this subcommittee, and I appreciate all of your participation on it.

Structure. Just to mention real quickly, the relationship to the main advisory committee. This is a subcommittee under the main advisory committee. There are actually five subcommittees that will be under the advisory

committee. The other four committees are the Clinical Pharmacology Subcommittee, which has already met; the Biopharmacology Subcommittee, which is scheduled to meet later in the summer; the Pharmacology and Toxicology Subcommittee, which is going to meet for the first time in June; and the Microbiology Subcommittee, which will also meet later in the summer.

We set up this structure because it was very difficult from the perspective of the main committee to focus on the numerous issues that are out there regarding the things that are regulated within OPS and throughout the center. It's very difficult to bring together 13-14 people with diverse backgrounds and have them focus on a specific issue. So we felt like the subcommittee structure was a good structure to have where the subcommittee could then make recommendations to the advisory committee as to specific areas that needed to be changed or specific recommendations for ways to go in the future.

The composition in the Manufacturing Subcommittee. Of course, you met all the members here this morning. Each of you met each other. And I want to thank Judy Boehlert for taking the time out to help us with this subcommittee. She was a member of our advisory committee and very, very helpful to us at looking at various issues having to do with chemistry review and other CMC issues.

So we appreciate her helping us.

Based on that, that's all I want to say. I do want to welcome the committee again. I look forward to a really exciting time working together.

Today basically what we're going to focus on is a lot on the GMP initiative. As I said, there are a lot of things under the initiative that I think working together with the subcommittee we can address, questions that we have, areas of manufacturing science that we need to focus on. So we have quite a full agenda.

David Horowitz and I are going to talk a little bit about the initiative this morning, and then we will spend the rest of the morning and part of the afternoon really looking at trying to prioritize how we want to go about working on some of the projects because there are numerous ones.

Again, as I said, at the GMP workshop two weeks ago, a number of issues were identified, a number of questions were asked by industry on how we were going to get things done, and we'd like to start with the committee actually helping plan how we need to tackle some of those things. So Dr. Hussain is going to walk you through this this afternoon after several presentations, beginning to look at how we want to handle this.

Tomorrow we're going to continue along with the

GMP, but we're also going to have an update on the PAT and an update on aseptic processing. The subcommittee has not -- of course, this is the first time it's met -- heard either one of these issues addressed specifically, but I think the PAT Subcommittee has sunsetted. There are a number of issues that came out of that committee which we'll present tomorrow. And then the aseptic processing update will basically just be an update of what we talked about with the advisory committee, as well as an update of the work that was done at the Product Quality Research Institute. So I realize you all have not been really briefed on this particular initiative that we had ongoing or this particular guidance. So it will just sort of be an update as to where we are and where we're going in the future.

So with that, I'm going to move on to my next presentation. Actually David Horowitz is going to give the first part of the presentation, and fortunately, David is here now. So we will go ahead and start with that. We wanted to, as I said, give you an overview of the GMP, where we are or where we're going. David is going to start out talking about how we got where we are and basically the reasons behind why the initiative came about. So I'll hand it over to David.

MR. HOROWITZ: Good morning. Thank you for

having me here. I'm glad to have an opportunity to address this subcommittee of the advisory committee, and I hope we have a chance to interact informally and a chance for me to answer any questions you may have or hear comments you may have.

I wanted to talk to you a little bit today about FDA's GMP initiative, which is really a drug quality initiative. It's broader than just manufacturing inspections and their oversight. I'm going to talk a little bit about some abstractions today, with a few specifics along the way. I'm going to talk about why FDA undertook this initiative, dividing that into some challenges in the environment and some opportunities. And not surprisingly, there's some overlap between those two. I'll talk a little bit about the scope of the initiative, and then I'll talk about the goals of the initiative. I'm not going to talk too much about the specific tasks and projects, but I'll give you a few examples to make it a little bit more concrete. And then Helen will follow up with some more of the specific projects that relate to these goals. Hopefully, I'll provide somewhat of a framework that explains why we're engaging in certain of the specific tasks that we're engaging in.

So I'll talk about external goals, and by that I mean goals for the drug manufacturing and drug

development industries, and internal goals for FDA, and then other guiding principles that may not be our major internal goals, but are part of our objectives here.

Why did we undertake this initiative? The first thing is that it's been 25 years since the FDA substantially changed its approach to the oversight of drug quality, and in particular, the last major change was the 1978 revision or comprehensive overhaul of the agency's GMP regulations. There have been other incremental shifts since then, including FDAMA's easing up on some of the requirements associated with manufacturing changes and SUPAC, which you'll hear more about later today.

But not surprisingly, there have been quite significant changes in the environment of pharmaceutical regulation over the last 25 years, and I'll talk about some challenges and some opportunities created by those major environmental changes.

The first challenge I think for us is the dramatically larger role that pharmaceuticals have come to play in health care and will continue to come to play in health care, as well as the larger number of products. Well, what does that mean for FDA? That means we have a larger number of drugs, a wider range of drugs, all different kinds of drugs in different classes. That creates a regulatory challenge for us. We need greater

expertise, for example, and greater manpower to deal with that.

This gives you an idea that our resources have not increased with the increase in the rate of drug development and the growth of the pharmaceutical manufacturing sector. What you can see from this is that our ability to conduct GMP inspections, manufacturing oversight inspections, has declined by almost two-thirds over the last 20 years.

So another related factor that's made it even more difficult for us to keep up with our available declining resources is the pharmaceutical industry has become increasingly globalized. There's also been an increase in foreign manufacturing sites. It wasn't true 25 years ago, the way it is now, that about two-thirds to three-quarters of the active pharmaceutical ingredients, really the most important part in many respects of the finished dosage form, are manufactured abroad, often in third world countries that are harder to get to and more expensive to get to and more difficult, therefore, to oversee with the same level of scrutiny.

We've also seen dramatic advances in pharmaceutical science, including the application of biotechnology to drug discovery and manufacturing. As I alluded to a moment ago, drugs have become more complex.

Manufacturing, therefore, has become more complex and diverse. That's a regulatory challenge for us. A large number of manufacturing supplements have been submitted to the agency and that number has only increased with the number of drug applications that have been approved. And yet, our resources have not kept up with that.

However, at least in the PDUFA area, to some degree, there's been an increase in resources available on the review side. But that's created somewhat of an imbalance, in my opinion, in the approach that we've taken to the oversight of the quality of pharmaceuticals.

There are some opportunities here as well. There have been major advances not just in the science of drug development, but in manufacturing science and technology throughout all manufacturing sectors. But you'll hear more today and you've probably heard plenty already that there is a great deal of opportunity within the pharmaceutical manufacturing sector and that much of the technological advances that we've seen adopted in other manufacturing segments have not yet been adopted and adapted in the pharmaceutical sector.

We've also seen significant advances in the science of quality management, including quality systems approaches. So 25 years ago, when we rebuilt those pharmaceutical GMPs, concepts of quality systems and

quality management were really in their infancy, to say the least. Since that time, we've seen a lot of development in the area, and FDA has made some incremental changes to its approach to regulation. In particular, I think the device regulations do an excellent job of incorporating the state of the knowledge and science when it comes to quality management. HACCP in the food area is a systems-based approach, in essence. More recently, without changing our GMP regulations, we have taken a systems-based approach to applying or overseeing our GMP regulations.

Other opportunities I think that have come from the change in the environment are dramatic changes in our ability to apply risk analysis and risk management. Some of our data analysis capabilities that have enriched risk analysis and risk management come about naturally as a part of the information technology revolution. There is data that we can analyze today that we simply could not have reasonably or easily analyzed 25 years ago, and that creates a wide range of opportunities for FDA and for industry.

Now, again, I think risk analysis and risk management is not foreign to foreign manufacturing, neither is it foreign to FDA. But I do think it's more systematically applied outside of the pharmaceutical sector and outside of FDA. Risk management approaches in

government on the regulatory compliance side are really gaining wide acceptance and they have a great deal of experience with this at EPA, at Customs, at OSHA, and everyone's favorite agency, IRS. We are just beginning, I think, to tap into this approach as a regulatory approach, and I think there are also opportunities for industry to focus its energy and resources using risk analysis and risk management.

Let me talk a little bit about the scope of the initiative now. It's not just drugs. You'll hear me using the word "drugs," but what I mean is broader than just drugs. The last bullet there involves all of the pharmaceutical centers, CDER, CBER, CVM, and the component of the agency that encompasses our entire field force of 4,000 or so people, the group that enforces and inspects our GMP regulations.

Going back up here, it involves more than just GMPs. It involves the submission, review, or the application component, chemistry and manufacturing controls, CMC. It certainly involves inspection, and it involves standard setting more broadly. Standard setting I think applies both in the review context and in the inspection context. To the extent we're interpreting and applying GMPs, we're setting standards.

I mentioned that it applies to veterinary

pharmaceuticals, as well as human pharmaceuticals and biological drugs.

It's a two-year initiative. It was first announced in August of 2002. We issued a six-month progress report in February of 2003. You'll be able to find that information on the FDA web site in great detail, if there's anything that I say that interests you.

First, I'll talk a little bit about the external goals, and then I'll talk a little bit about our FDA internal goals, and I hope you'll see some parallelism between the two, or at least some connection.

We want to facilitate and encourage the adoption in pharmaceutical manufacturing of the latest advances and innovations in three main areas. These are really the three themes running through the GMP initiative: manufacturing science and technology; quality management, including quality systems approaches; and risk management approaches.

Now, why do we care about that? CDER's mission, which is a part of the agency's mission, is to make safe and effective drugs available to the American public, and we believe that facilitating innovation and availability of safe and effective drugs are consistent with these objectives here.

There are a bunch of working groups that Helen

will talk more about that are focused on our internal tasks, and I'll relate those to our internal goals, but I won't stay too long on this slide because I think Helen has it as well.

Primary internal goals. Well, the first piece, not surprisingly, is the quality systems piece. We need an internal quality systems approach. We need to achieve greater coordination and synergy from better integration of the submission review and our facility inspection components. In other words, the application review and the inspection folks need to be integrated in a way that I think we haven't fully accomplished. We need to generally enhance the coordination between the field and the centers and among the centers that regulate pharmaceuticals.

Now, these are all consistent, we believe, with a quality systems approach. This kind of integration and looking at the totality of our approach to regulation is important. We need to enhance the consistency in applying science-based standards for both the submission review and the facility inspection programs. We've formed, toward this end, a work group in internal quality systems, and there is a great deal of energy that will be devoted to this task in the coming years.

The second major internal goal, implementing systematic risk management approaches to all aspects of

drug quality regulation. That includes standard setting, it includes review, and it includes inspection.

Now, we want to identify the parameters and the processes that are critical for drug quality, as well as those that are insignificant. Now, this is a key piece of risk management for us because this is a risk assessment technique or activity that will allow us to prioritize risks and better focus our energies internally for setting standards and for focusing our resources. We want to ensure that FDA resources are used most effectively and efficiently to address the most significant public health risks. As you saw on that chart, we don't have resources to burn. We need to know what's most important. We can't take the risk that we'll be focusing on some moderate risk and trying to abate that while we're ignoring something that could be more significant, a risk to the quality and safety and effectiveness of drugs.

In general, what we want to accomplish is adjusting the level of regulatory scrutiny so that it is commensurate with the risk, and there a variety of tasks that we're working on that pertain to that.

The first is work planning. We want to look at how we allocate our resources for inspection. We want to have a systematic risk-based model that allows us to prioritize our inspections according to the risks

associated with the manufacturing going on at particular inspection sites. So we want to be smart about where we go, but we also want to be smart about what we look at, and that's going to include changing our guidance that we give to investigators, our compliance programs that tell them what to look at when they get there. As we have more sophisticated process knowledge and we better understand what's important and what are the critical parameters, we can focus our investigators, when they get to the high-risk sites, to focus on the high-risk things.

So I mentioned earlier adjusting the level of regulatory scrutiny with the risk. Related to that also on the review side, I think, is the comparability protocols and making sure that the application and supplement requirements for submission are consistent with risk posed by the manufacturing change.

Similarly, changes to the approach to regulating electronic records, known as Part 11, are consistent with this risk management framework. We don't want to have regulatory requirements that are completely out of sync with the risk posed by those topics which the regulatory requirements are intended to address.

The last and perhaps most important internal goal for this group is enhancing the scientific underpinnings of all aspects of the agency's regulation of

drug quality. That means, in part, more science and risk-based manufacturing guidance. It means FDA learning through various opportunities from the process knowledge that can be gained from the design and development phase. What we've learned is that industry has a lot of this knowledge and gains it when they're designing and developing new drugs. Sometimes that information isn't shared with FDA because it's not required to be shared with FDA, and we think it would be very useful to have that knowledge shared so we're operating from the same page in understanding about what are some of the critical processes and parameters for manufacturing.

Also consistent with enhancing the science in the agency is providing greater opportunities for specialization, for training, and cross-cutting teams. Tasks that pertain to beefing up our science are developing a specialized core of pharmaceutical investigators in the field, known as the pharmaceutical inspectorate, to adding product specialists when appropriate on inspection teams, and the PAT initiative, which you'll hear much about.

There are some other internal guiding principles which overlap with many of these three internal goals that I talked about, and I'll just speak about these briefly.

The first is improved internal and external

coordination. Well, I don't think we can do any of the other three things I talked about unless we can improve those things, and a lot of our activities pertain to improving those communications, like we're here today. Scientific workshops and advisory committees are crucial to us achieving greater transparency and better communication.

We're developing an easier to use dispute resolution process to raise scientific and technical issues that arise during an inspection where scientific issues and disputes come about.

We want to do what we can to make sure that people better understand what a 483 is. For those of you who don't know that agency phrase, that's the list of inspectional observations that an investigator hands out at the conclusion of an inspection. It has come to our attention that those observations have been widely misinterpreted sometimes because there is not sufficient science-based guidance, and these observations of one investigator are interpreted and applied as though they are the agency's official position on what is required for drug manufacturing.

Finally, center review of GMP warning letters we think will help us improve our internal communications, as well as, to some degree, our external communications. What I mean by that is with the center's being involved in

overseeing and working with the districts in the field on the warning letters, there will be greater opportunities for the field and the center to exchange their views, to raise any disagreements, and to resolve them.

The last two items I wanted to talk about that are guiding principles are international harmonization, which has become increasingly important and, from what we learned at the workshop, is quite important to the industry. We're going to be working through the ICH forum and other international fora to make sure that the approach that we're striving toward will be consistent with our goals for international harmonization.

And last and perhaps most important, we're never losing sight of the strong public health protection, which is the main purpose of this initiative and the main purpose of FDA's goals and objectives. We will not take the risk that this initiative will interfere with strong enforcement of existing standards, even while we're examining and revising our approaches. So there's not going to be a moratorium on all quality regulation. We do expect that these principles will immediately infuse our thinking, as I think they have for many months now.

Thank you very much. If you have any questions, I'll be glad to answer them when there's an opportunity.

DR. BOEHLERT: David, I think we have an opportunity right now, if there are any committee members who have specific questions, because we're well ahead of time on our schedule.

MR. HOROWITZ: Please.

DR. SINGPURWALLA: I have a comment and a question. The comment is on your chart number 5 which shows the proportion of inspections going down.

MR. HOROWITZ: Okay. That one I know by heart.

DR. SINGPURWALLA: I just would like to make a comment that that in itself is not too bad because as things improve, you probably want to monitor less.

MR. HOROWITZ: I think that would be true if we felt that things really had improved dramatically at that rate over the last 25 years, but I agree with you that we ought to get to a point, through these other techniques, that the level of inspectional resources we have are sufficient if we use our resources smartly.

DR. SINGPURWALLA: That's just a comment.

MR. HOROWITZ: I appreciate it.

DR. SINGPURWALLA: The question pertains to my favorite agency. I'm curious. How does the IRS use risk analysis --

(Laughter.)

MR. HOROWITZ: Well, they wouldn't tell me any

trade secrets, so I can't pass them on to you. But in general, what they try to do is similar to what all regulatory agencies who use risk management do. They try to identify risk factors to better target. So, for example, if they determine that through various empirical and experimental methods that people who have home offices are more likely to phony things up, then they would target areas like that. That's obviously an oversimplification on my part, but in general, they devote a great deal of energy to identifying risk factors through various surveillance techniques, which includes data analysis primarily in their case.

DR. SINGPURWALLA: Thank you.

DR. BOEHLERT: Dan.

DR. GOLD: Mr. Horowitz, I also would like to address slide 5. You show a reduction of two-thirds in the number of inspections. I was not aware the field force had decreased by that heavy a percentage. In fact, I'm not aware that they decreased over this period at all. So what would be the explanation for this?

MR. HOROWITZ: Well, I think there are a number of explanations. Over the last 25 years, the agency's legislative mandates and the complexity of the world has grown. The scope of FDA's oversight has grown dramatically over the last 25 years, counterterrorism, biotechnology.

Many of these resources have been pulled away to other things that were not on the horizon in 1980.

However, there's one other important factor. Some of these drug inspectional resources have been shifted to the preapproval inspection program. That's covered by PDUFA. As I mentioned earlier, PDUFA has changed the landscape to a large degree of the oversight of drug quality regulation.

There has been a large increase, also related to the 1980s' generic drug scandal I think, in increasing preapproval scrutiny. I think in part it has come at the expense of post-approval, comprehensive, systems-based GMP inspections.

DR. GOLD: But if you were to add preapprovals in and if you were to add the international inspections in, which have increased substantially during this period, what would the normalization figures be?

MR. HOROWITZ: I don't have the exact numbers, but first I can tell you that the number of international inspections has not increased significantly. The number of international drug GMP inspections that are not preapproval inspections is very low, very low indeed. It would be just a small blip on that chart. So if you added the foreign preapproval inspections and the foreign domestic, you would still see the same trend. The line wouldn't be as steep,

though.

DR. GOLD: Are you excluding from those international inspections API inspections?

MR. HOROWITZ: Those inspections are just domestic, what I put up, the chart --

DR. GOLD: No. I'm talking about the summary you just gave. You said inspections have not increased dramatically overseas. Are you excluding API inspections from that?

MR. HOROWITZ: API inspections are often part of the preapproval inspections.

DR. GOLD: Yes, I realize that.

MR. HOROWITZ: And those, of course, with PDUFA have increased both domestic and foreign. I am saying that there has not been a dramatic or significant increase in API inspections that are not part of preapproval. We don't have the resources. We don't have the capacity to adequately monitor foreign manufacturing, particularly when it is not part of the preapproval inspection program.

DR. GOLD: Thank you.

DR. DeLUCA: David, it seems that table 5 has drawn some attention here. I guess the question I would ask is the numbers decreased here, but what about the time devoted? If you're spending more time on an inspection, then maybe it's balancing out.

MR. HOROWITZ: Yes. I have heard and I have seen evidence that drug GMP inspections have tended to take a little bit longer over the years, and some of you may have personal knowledge of that. As the complexity of manufacturing has gone up, in part that has resulted in longer inspections, and some have said that there's been regulatory creep in that regard.

But I've seen the numbers. I don't have them charted, but I've seen the numbers and the trend is still the same. The hours that are available or the FTEs that are available for this inspectional program have significantly and consistently declined over the last 20 years, and that's something we need to make up for by being smarter about what we focus on.

DR. BOEHLERT: Gary?

DR. HOLLENBECK: David, this is an impressive agenda. It's very nice to see all of these itemized and laid out in front of the group. I'd just like you to comment on the two-year time frame. You mentioned that it's a two-year initiative.

MR. HOROWITZ: Right.

DR. HOLLENBECK: So what do you mean by that and what do you expect to accomplish during that period?

MR. HOROWITZ: I'm glad you brought that up. I can't put anything over on you guys.

The truth is that this is a two-year initiative and that doesn't mean we'll accomplish all of these goals, stop this, and then go back to what we were doing because we all know this is really a radical shift in what the agency has been and will be doing for many years to come. In two years, we hope to be well along the path and have established the path to continue down these roads to better accomplish all these objectives. We're not going to just shut this down in two years, nor could we.

DR. LAYLOFF: I have a question and a comment. My question is over the 25-year period, how has the official establishment inventory fared as the industry consolidates across the country?

MR. HOROWITZ: Well, that's an interesting question. You'd think with greater consolidation, the establishment inventory would decrease and it would make it easier for FDA. We haven't really seen that. Even though there might be one corporate parent, in many cases they aren't shutting down manufacturing sites. As more and more drugs come to market, they haven't been shutting down the actual site. They've just been putting it under different management.

But the biggest strain for us has been, believe it or not, the growth in medical gas repackers. There are about 6,000 domestic firms that manufacture, repack, or

test drugs. About half of them -- and this was not the case in 1980 -- are these facilities that take medical gas from large stand tanks and transfill them into smaller tanks, and they're subject to GMPs. In the late '80s, the resources that were being devoted to that were climbing dramatically, and it was taking resources away from the higher risk manufacturing establishments.

Since about 2000, we've significantly cut that back and those resources have been put back into what I might call the traditional pharmaceutical manufacturing oversight.

DR. LAYLOFF: And one comment. I think FDA has been strongly involved in risk management of products since 1938.

MR. HOROWITZ: Correct.

DR. LAYLOFF: Actually we led everybody else.

MR. HOROWITZ: Absolutely.

DR. BOEHLERT: Nozer, did you have another comment?

DR. SINGPURWALLA: Just a general comment. It's based on your very nice presentation. I get the general impression that when you use the words "risk analysis" and "risk management," you're taking a very, very broad-based view. I have difficulty separating it from classical statistical analysis. So I just want to go on

the record as saying that when you use the words "risk analysis," it encompasses a very broad spectrum of things, and perhaps we may need to sharpen our understanding and terminology as we move along so that we can all communicate at the same level.

MR. HOROWITZ: Yes, I think that's an excellent point. For the purposes of this presentation, we wanted to sort of give a broad overview and operate on the more general levels. But we recognize internally that a great deal of work still needs to be done on focusing and sharpening our approaches and defining what we mean not just by risk management and risk assessment, but in fact what we mean by risk, what we mean by drug quality. And I think you'll be hearing more about that in the coming months.

DR. SINGPURWALLA: Just to add to that, when people in finance talk about risk, which they use quite a bit, all they mean is variance or volatility. That's the word they use. That's a cause of risk. That itself is not risk.

MR. HOROWITZ: Yes. There's a great deal of academic and industry literature applying risk and risk analysis to the financial field, to the insurance industry, even in the legal field to litigation in health care, for example. In general, one of the common threads is they

talk about the severity and the probability of a particular harm. Those are two of the elements we're looking at in risk.

But, of course, one of the challenges in applying risk to drug quality for us is what is the harm. Is the harm risk of violating some regulation? Probably not. Is the harm the risk of reduction in drug quality, and if so, what is drug quality? Some have said, well, drug quality is fitness for use. Well, what is fitness for use?

So these are all questions that we're grappling with, and we appreciate your pointing out that a lot more work needs to be done in this area and we expect to have additional public discussions like this one as our thinking evolves.

DR. BOEHLERT: Any other questions? If not, David, thank you very much.

DR. DeLUCA: I'd like to just add one thing.

DR. BOEHLERT: Wait a minute.

DR. DeLUCA: Looking at this, as was already pointed out, this is quite an ambitious agenda. I can't help but think as an academician that we're at a time, over the last 10-15 years, where the area, what we're talking about here, manufacturing science and technology making advances, is an area where in our colleges of pharmacy this

emphasis has been declining. Not only has pharmaceutics been declining at the expense of other disciplines in research, but as you start moving in this direction, which I think is very important -- it's music to my ears -- I can't help but think how this is declining and there needs to be some effort by the industry and the regulatory agency to try to impress upon our academic institutions that this is an area that is in need of emphasis and maintaining excellence in this area. That's being lost, and I think my colleagues here might add some comments to that.

DR. HUSSAIN: Judy, may I? I think that is a very important point, and one of my hesitations and concerns has been did we start a bit too late because I think in a sense industrial pharmacy infrastructure in academia has dwindled leaving behind a situation where I think we may not have a critical mass today coming out of schools, and that is a concern. The agency is working with the National Science Foundation also highlighting the need for this. In fact, I probably will be speaking to the deans of schools of pharmacy to reemphasize the need for this, but also trying to bring chemical engineering departments into this. So I think we are very much aware of this challenge, and I think we will seek your help to bring awareness to the right people.

DR. PECK: The point is well taken, Pat. We

have been approached by several industrial units within the Midwest to try to blend pharmaceutics and regulatory affairs, and we have recently established some sort of academic approach to bridge the gap of understanding regulatory affairs and drug product design, process design.

Ajaz was with us last week as we did some specific training on PAT. It came out of that that we need to look at centers of excellence in pharmaceutics that we have left, one.

And two, we have to get others to realize the importance of pharmaceutics. I think in our educational programs over the years, we've emphasized the product and where it goes, and it goes to a patient. We have to relook at that as we approach the manufacture of products and have a true appreciation of this effort for quality. So we have a challenge for those of us who are still active in this kind of education to make certain that people understand where the product goes.

DR. BOEHLERT: Any other discussion?

(No response.)

DR. BOEHLERT: If not, I thank the committee members. I think we brought up a number of issues today that came to my mind, at least when I reviewed the background material, not the least of which is defining what we mean by risk management. So it's a good start to

our discussions. Thank you.

Helen has been standing in the wings.

MS. WINKLE: While he's working on the computer, I'm just going to start a little bit. I'm going to just continue with FDA's perspective and where we are with the GMP initiative and try to go through the various task groups and just give you a quick update.

First of all, I want to thank David for coming today and talking a little about the initiative with us. I think it's really important, as the subcommittee moves forward, to realize the need for all different parts of the agency to work closely together with the committee as we look at manufacturing science and at other aspects of the initiative, as well as other aspects of how we're doing manufacturing. The Office of Compliance and the Office of Pharmaceutical Science are working very closely together to make the GMP initiative happen, but we're also working very closely to try to make other parts of the regulatory process work better within the center.

But we've worked closely too with the field organization, with the Office of Regulatory Affairs. We had hoped that John Taylor could join us today to talk a little bit to the subcommittee. Unfortunately, the timing was bad. But as the subcommittee continues to meet over the next few years, I think you will see a lot of input

from the Office of Regulatory Affairs, as well as from both the Office of Compliance and the Office of Pharmaceutical Science. So I wanted to really again thank David for helping us introduce this subject this morning.

As I said, I'm just going to catch you up as to where we are and we can probably do it without the slides.

This is again the slide that David showed on the various GMP task groups. I wanted to put it back up again because I think it's important to at least keep these groups in mind as we talk about the initiative and how we're going to focus on it with the Manufacturing Subcommittee.

As you can see, basically the group is made up of a steering committee. The steering committee is across the agency. It includes all of the different centers who are involved in pharmaceutical manufacturing and regulation, and also Dr. Woodcock is the chair of that committee.

There are 14 task groups within the committee. Some of these task groups are not completely active. I'll talk a little bit about them, though. As you can see, there's a training task group on here, and all of the other task groups I think in some way will contribute to the training task group. So until they've really completely identified their working plans and where they're going, we

won't have much from the training task group.

Also the evaluation group. Every initiative needs an evaluation group, and this group, although it has met, will of course not focus until some of the other tasks are completed.

The question that came up was how long the entire initiative is slated for. Obviously, there's a lot of work here. As I go through these various task groups, you'll see all that we're working on. David has already touched on several of them, but obviously two years isn't enough to complete every one of the tasks. This is a continuing improvement process I think both within the center, as well as in industry, and we'll be working hand in hand for many years out to make these improvements.

The first task group I wanted to talk about is the Part 11. I think David already touched on this quite well. Basically the goal is to change the approach to 21 C.F.R., Part 11 and incorporate the principles of the cGMP for the 21st century.

Again, there is a lot we haven't done in the last 25 years that has focused on this area except put out, I think, regulations which was confusing to everyone. So we're trying to now go back. We have put out a new guidance on this to industry. We want to amend 21 C.F.R., Part 11, both the rule and the preamble, and actually have

a narrow interpretation of the scope, making sure that everyone understands that it doesn't cover systems incidental to creating paper records. It's really focused on the e-records, and we're trying to clarify that. We realize that that clarification is very necessary. Joe Famulare, who is sitting at the table, actually is heading up this work group and has done quite a bit already to help clarify in this area.

Manufacturing science. The goal here is to ensure high efficiency and quality of pharmaceutical manufacturing and associated regulatory processes and to enhance FDA's expertise in engineering and technology. I think that it's very important, the second part of this goal, from the subcommittee's perspective, to help us in the agency to have a better understanding of what we need to know in the area of manufacturing science and to help us to understand those technologies that we need to have a better understanding of and be able to apply those in the regulatory scheme.

We did have a workshop in April of 2003. I'm sure many of the people in this room, as well as people on the committee, were at that workshop. It was a very important milestone, I think, for us in the agency because it was one of the first times we've really gotten a lot of information from industry and other stakeholders on what

really we need to focus on. And we are in the process now of going through that information that came out of the workshop and evaluating the information and trying to determine where that fits in our planning for the next stages of the initiative.

Also, we've talked about manufacturing some at the advisory committee, and as a result of that, we have set up this subcommittee. As I said earlier, the subcommittee I think is going to be very valuable to the agency in helping address many of the issues on manufacturing science.

Changes without prior approval. The goal is basically here to identify the opportunities to allow post-approval manufacturing changes without FDA review and approval prior to implementation. This is very important for a number of reasons, I think, resources being the main reason both on the industry side and on the agency side. But there are other important aspects of this as well. Hopefully, we'll be able to look at this, both at the subcommittee level and more at the agency level, to find other things that we can do to help simplify, as well as make changes more effectively.

We already have the comparability protocol guidance, the draft that's come out. At the workshop, we heard a lot of questions on this. So there's a lot of

clarification we need to have here. That guidance is up on the web.

483 communications. David spoke to this as well. The goal here is to determine proper mechanism for communicating deficiencies and inspectional observations to industry. In many of the conversations I've had with various groups on the GMP initiative and what it means to industry and other stakeholders, there have been a lot of questions on how we really communicate the observations on the 483, a lot of questions as to what kind of effect they have on our manufacturing processes, as well as on how we regulate internally. So we really need to clarify that. We have written internally additional language for the 483s to help clarify that they are observations that are made by the inspector, but there's a lot more education and training that needs to get out there to the industry on what these communications actually need to be. So we'll be working a lot on this in the area.

This group has actually been folded into the dispute resolution group, and I'll talk a little bit about that in a minute.

But this has been important because, again, there are a lot of questions in this area on what we're saying in the observations, and I've heard from industry that many of the companies will read through the

observations and actually make changes in anticipation of inspections to accommodate to the observations that have been made in other firms. So it's an area where we really need to think more about how best to get this information out.

Warning letters. The goal here is more scientific review of warning letters before they're issued to the firms and to ensure consistent application of policies and procedures. We're in the process now of implementing a new internal process so that we can get more scientific review of warning letters before they're issued. In the past, there has not been input from the scientific side or actually in CDER from the CDER side as to what the letters may say and whether they're really focused on relevant scientific issues that need to be addressed. So we're going to go back, look at that process. We'll start a process where, in fact, some of the reviewers can actually have an opportunity to look at the warning letters, along with our compliance folks in the center, to make sure that we're really addressing significant problems that need to be addressed.

Dispute resolution. I already mentioned this. The goal here is to develop consistent policies and procedures for formally resolving scientific and technical GMP issues and improving transparency of such procedures.

We're in the process of developing the guidance. Actually David and I chair this working group. This was one of the things that people call low hanging fruit, and actually it's at the top of the tree.

(Laughter.)

MS. WINKLE: We're having more trouble with this particular working group than we ever anticipated.

But I think we're to the point where we do have a process identified, where we'll be putting a guidance out hopefully in the next few months. What we plan to do is have a 12-month pilot with the dispute resolution process in order that we can evaluate the process and determine where best to make improvements to it. It's been very difficult. Again, we were looking at having both an informal process, as well as a formal process, and basically we're focusing now more on the formal process so that we can get something out there that everyone can take advantage of.

Risk management. I think the questions here were very good. I have had problems myself because I think when we talk risk management, every one of us is talking something different. But as David tried to explain, we definitely need to better define risk management. But as far as this particular working group is concerned, they really have a goal to ensure that systematic risk

management approaches are applied, whatever we identify as being the real risk, that we can apply so that we can better allocate resources, actually select sites for inspections based on those risks, and determine the scope of the GMP programs for both human and veterinary drugs. This is really important.

It's a big area for us and one that's going to be, I think, very complicated for us to really determine where to focus our resources. We hope to work with this group a lot in being able to help us to identify and maybe even define risk management and help us to identify what we need to be focused on as we try to apply this to actual inspections.

Pharmaceutical inspectorate. The goal here was to establish a staff of highly trained inspectors who will spend the majority of the time doing drug inspections on high-risk firms and have a close working relationship with the centers. This has not been the case. When we talked about the decrease in the number of drug inspections, as David said, there's a number of reasons why this has happened. We need to have a better handle on directing these inspections and really sort of get the bang for our buck when we send our people out. So having an inspectorate will make it possible for us to have better trained people who can do inspections more efficiently,

more effectively and facilitate the opportunity to work closely with the center. This doesn't happen as much as we'd like to see it happen. I think it's very important that you have that interaction between the inspectorate and the people who are doing the reviews, the people who are in the center working them from the regulatory aspect. So this is one of the things we hope to accomplish.

We're looking at approximately 50 people. Where we are now with this initiative is that we have been working on an expert PD for the members of the inspectorate and an agreement between the centers and the field. We're looking at approximately 50 people in this inspectorate. We will probably, in the next year, have identified 25 of these people and we'll begin to work with them to do more training. What we will do is come up with a curriculum for additional courses, additional information that they really need to be able to do an adequate job in doing inspections.

Product specialist. In order to sort of supplement the inspectorate, we'd like to be able to utilize some of the people we have in the center who have a lot of knowledge in particular areas. Obviously, every inspector can't be trained in every aspect of manufacturing science, but we have experts in the center in a variety of places that we're hoping to be able to include on an inspection team that can help in strengthening the

consistency of the reviews and to ensure that submission reviews and inspections are better coordinated and are synergistic. We're still in the process of identifying who these people will be. In the review areas, we've tried to narrow down who some of the specialists that we have are, people who have particular expertise in certain areas of manufacturing, and begin to utilize these people more in looking at some of the applications, as well as getting involved in the inspections. We have developed a concept paper which is up on the web.

Team biologics. I didn't want to talk much about this because I really don't know a whole lot. David is probably in a better position, but there's already been a lot of work that's been going on with the team biologics program. The improvements to this program started before the GMP initiative. It's basically been rolled into the initiative, but with taking on the new products into CDER from CBER, it really is going to be necessary for us to be more involved in this program and to have a better feel for how we need to interact with the program and adopt some of the principles of this program into our own inspectional area.

Basically the team biologics program is already in the process of adopting an internal quality management system and developing metrics to determine the impact on

industry. I think this is really important. This is something we need to think more about in the center, these metrics. Standardized training and qualifications of core team members. They've implemented a risk-based work planning, and they've increased their communication between headquarters and the field. As I said, there are several things from here, I think, that we can learn and incorporate into the CDER program.

Quality systems. This is an area that still needs a lot of work with the working groups. We actually have two working groups, an external and an internal working group. We're still trying to determine how best to apply the internal knowledge that we have to be able to see where we're going with this. Some of it is we've been looking at whether we need to rewrite our regulations, whether we should leave the GMP regulations the way they are. Maybe there are parts of it we need to do. We also are looking at getting guidances out in this area. So we really know that there's a broader implementation process that needs to be incorporated, but also when we look at that, it goes beyond the scope of the GMP initiative. It actually affects how all of us do our work in the agency. So it's difficult to narrow down on that part that we need to focus on.

We have, though, as a part of this, begun to

implement a quality systems approach in how we conduct CMC reviews. I hope at one of the future meetings that we can talk more about some of the things that we've done as far as the quality systems approach in our Office of New Drug Chemistry and actually get some feedback from you. So this is an area I think you're going to see more and more. As we in the center and in the agency get a better handle on what the quality systems approach is and how we plan to implement it as far as GMPs, I know that we'll be coming back to the subcommittee.

International. David has already talked about this. The goal here is to have internationally harmonized approaches to assure drug product quality and encourage technological innovation. He mentioned ICH in July where we'll begin to talk about some of these approaches. Also, there are other venues too that we'll begin to look through. We actually probably even appreciate recommendations from the committee as to where we might want to look in the future to improve that international harmonization.

There is a task group on here, contracts management. Basically this group was set up to expedite external studies of key issues to be addressed by the GMP initiative. We have several contracts that are currently being researched in the agency. One is for effective

quality systems practices. We actually had planned to have a number of briefings on what we think are effective systems and to better educate our people in this direction. We also are looking at some benchmarking projects. But neither one of these contracts has been let as of right now. So we're still in the process of talking about them internally within the agency.

Other. I already mentioned evaluation and training. Both of these will be based on what comes out of the other working groups.

Next steps. I talked about these, and when I talked earlier this morning, I talked about the role of the Manufacturing Subcommittee. I think there are a number of things the subcommittee can help us in doing to move forward. Obviously, there are numerous activities that you all can help us in supporting and helping us better think through them. I mentioned today that in the agenda we're going to begin to work out a plan for the subcommittee. Working together, I think we can determine what we need to prioritize.

Also, I'd like to ask the subcommittee to help us recognize other areas that we might want to consider that we may not have thought about. When we sat down and originally set up the initiative, we looked at those things that we felt were the most relevant to helping us make

changes in how we looked at issues, but I know there are things that we probably haven't touched base on, and I think over the next few meetings, we can begin to identify a number of those issues as well.

Again, I think it's an important group here. I look forward to working with you all in this area. This morning David and I have given the FDA perspective. Dr. Raju is going to give an academic perspective, and then Mr. Lavin will give the industry perspective from GPhA, and Gerry Migliaccio from the PhRMA perspective. I think this will help us all think through where we need to be going, how we need to plan out the next steps. I think they will all begin to weave together and we can begin to see the issues and identify those issues that we feel that this subcommittee can really give us some answers to.

So with that, I'll turn it back over to Judy. If anybody has any questions, I'll be glad to answer them.

DR. BOEHLERT: Any questions or comments? Dan?

DR. GOLD: Helen, one area that would leverage the available resources within the agency that you did not mention or David did not mention are mutual recognition agreements. I haven't heard anything about them recently. They would obviously relieve some of the inspectional burden. Why are they not part of this group of initiatives that you've mentioned?

MS. WINKLE: I'm going to let David or Joe answer that. They probably have a much better answer than I do.

MR. FAMULARE: As you're probably well aware, we were well on the task of a mutual recognition agreement with the European Union, and that is a very resource-intensive effort in and of itself in terms of finding each other's authority's equivalent. In terms of saving resources, the actual equivalence determination itself is a very resource-intensive task which, to this date, has not been able to be finished because of that resource involvement.

But all is not lost there. We are looking for other approaches in terms of taking advantage of what we can from our international partners. Some of that was even brought up generally at the PQRI/FDA joint meeting several weeks ago in Washington in terms of how we could harmonize, how we could take advantage of other organizations such as the pharmaceutical inspection cooperation scheme and so forth which could make us get to some of that information sharing in maybe a less burdensome way. So there's more to come in that area, but right now mutual recognition is burdened by the resource strain.

MR. HOROWITZ: If I could just add to that. The spirit that motivated the MRA, I think, is alive and

well. The problem is that the equivalency determination proved to be so burdensome, and the implementation of the MRA that the EU insisted on required that all of the EU nations be found equivalent before the agency could gain any of the resource benefits of starting to implement on a country-by-country basis the MRA. Particularly now that the EU has expanded with several additional less-developed countries, that approach is not workable.

So at the moment, we're looking at other ways and other opportunities to leverage the results and oversight of other foreign inspectional bodies and working through harmonization and other techniques to accomplish the same objectives.

DR. LAYLOFF: Another thing, Dan. I think that products in the United States are part of a web which involves the FDA, but it also involves very heavily tort law. So you can't look at it from a monolithic point of view that the FDA is the sole controller of product quality. It's actually the whole legislative and societal environment that controls it, and I don't think we have that in other parts of the world.

DR. BOEHLERT: Nozer?

DR. SINGPURWALLA: Question. When you issue a 483 communication, is this open to the public or does it only go to the particular organization? Because there is a

risk-benefit in that. If you tell everyone, then the others are aware that this has happened and so they will take action. But at the same time, the particular industry that has received the 483 suffers because their reputation could be tarnished. So what is the disposition of a 483? Is it public?

MS. WINKLE: It is public, and you couldn't have said it better than we would say it here. I think that industry would agree with you that this is why there are a lot of questions on the 483 is because their reputation can be tarnished, as well as what I was saying. A lot of people take advantage of that information to utilize as a way of trying to see what direction the agency is going as far as their inspections are concerned and what are some of the scientific and technological areas that they're focused on. So, yes, they are public.

MR. FAMULARE: If I could add to that, I think one of the important issues that the work group looked at was the fact that these are the investigators' observations just as they're doing the inspection, and they haven't gotten the review of the agency or been determined to be actual violations of the law, the advantage being, of course, the fact that they are available to the general public from the perspective that you looked at it, but the disadvantage is that many companies feel that once that

observation is there, that they will implement it, not only in that company but in other companies, without a full airing of the issues to see if it's actually appropriate at the end of the day. So that's the problem that's being grappled with.

MS. WINKLE: One of the things I failed to mention is at least many of these different task groups are sort of intertwined with one another, and one of the things with the 483 group and how we communicate sort of intertwines with what we're doing in dispute resolution. It's to give now industry a mechanism for being able to come in and dispute some of those observations, the science behind the observations. And what's going to be very important to us in the agency is then to be able to communicate that information out publicly as well so that industry has a better opportunity to see why we have made certain decisions or observations.

DR. BOEHLERT: I think next on the list was Efraim and then Tom.

DR. SHEK: Yes, but I wanted to talk about the international --

DR. BOEHLERT: Okay. Tom, do you want to make a comment to that? Then go ahead.

DR. LAYLOFF: The dispute resolution provides a CA/PA procedure which is an internal quality system on your

training of investigators. By reviewing 483s and going through the dispute resolution process, it gives you a closed loop to train the investigators not to do that again.

DR. BOEHLERT: Before Efraim, Pat, you wanted to comment?

DR. DeLUCA: Yes, on the 483. I just would follow up what Tom said.

When I teach my course in parenteral technology, I use the 483 as a springboard because you can cover an awful lot of territory just by going through a 483 covering a number of issues.

I guess one of the things that I would like -- and I thought Helen had said something about really understanding the 483 -- is that what are observations and what are violations. And I don't think that comes out too clear. I'm just wondering if that could be a focus. Is it an observation or is it a bona fide violation?

MR. FAMULARE: Anything on the 483 is an observation. Whether it rises to the level of a bona fide violation can only be determined once the agency further reviews that and makes a determination. For example, I don't have a representative. Well, we have Mike here from ORA. But one of the efforts that ORA at least made in the past towards this effort is to send a letter to each firm

after the inspection and review to tell you what the outcome of the inspection was. Now, that wasn't a line-by-line listing of how you made out on each 483 observation.

But the issue and the fact still remains, as Helen brought out, that it is a public document so that if something on the 483 turns out to be, after evaluation of that initial observation, really not appropriate, as Helen said, all of industry may see this and say, well, this must be the way to go and follow along that way. So one of the things that was done by this 483 committee folded into the other committee was to put a statement further explaining the observation nature, that it's not a final agency conclusion.

DR. DeLUCA: Is there some link in the public record here or availability between the 483, what's written by the inspector, the letter from the FDA, and the response by the industry? It seems there should be some kind of linkage there to tell the whole story.

MR. FAMULARE: Well, the documents are available through FOI. The thing is that they're not all released in sequence. One thing about the 483, when it's given to the firm, it's releasable except for certain information, confidential, commercial, and trade secrets so that it's out there before the company has responded and so forth. So it's out there at the very beginning of the

process.

MS. WINKLE: Two points I'd like to make is we've had this discussion ourselves within the dispute resolution working group quite a bit. One of the things we feel is very necessary in the whole process is that when an observation is determined by the field, before it even goes into dispute resolution, to not be a viable or accurate observation, that they will also put something out as an addendum to the 483 that says that this observation has been removed or it didn't have the scientific validity or whatever. We haven't come up with any words or how we're going to do it. But I think it's really important that we indicate that when an observation comes off a 483, that everyone knows it, and we don't publicize that now. The firm may know that that observation is no longer on the 483 or it's been agreed to by the district to remove it, but the public doesn't. So that's one part of it.

But I think it's really going to be important for us to find better ways to communicate with industry about the observations, that these are observations, the importance of that, because I think that the interpretation is they are violations in many cases. And I think that's why industry goes to the extreme that they do go to to try and make corrections because they don't want those same violations or those same observations when inspections are

done. So we have not done a good job, I think, internally within the agency of really communicating what these observations mean.

So I think when we talk 483 communications, we're talking much more than the 483 itself. We're talking about how to get better information out to the stakeholders on what we mean by the document.

DR. BOEHLERT: Efraim.

DR. SHEK: To get back a little bit to the international initiative, I believe it's a great opportunity for society both for the regulatory agencies, as well as for industry.

As all of us know, we are spending a lot of energy on what we call the common technical documents, but if you look at them really critically, there are not too many documents that don't have to be rewritten between requirements in the U.S. and international requirements. What is basically left many times is just the frame, the outside frame, and it's worthwhile to try to harmonize. Maybe that will be an easier step than to get the mutual recognition to harmonize, as much as we can, the regulatory requirements which will enable us to come to better agreement and use the common technical documents.

MS. WINKLE: I agree. Thank you. I think there's a lot that we have to do here. It's going to be

determining where we need to focus our efforts. That's why I put other venues on there because I think we have not completely determined ourselves how best to make some of the international changes we need to focus on.

DR. BOEHLERT: Gary?

DR. HOLLENBECK: Helen, I'd like to focus on the empty box there, the training box. I heard your explanation, and I think it was something like we'll see where the other boxes end up and then we'll do the training initiative. I guess my perspective you should start now. Maybe I'd like to hear your comments as to why the training and education aspects of this initiative haven't been started yet.

MS. WINKLE: Well, in some ways I think they have. I just don't think we have an identified task group yet. I think each one of the working groups has some type of education process going on. Identifying, though, who we need to train besides industry is going to come very shortly through the various working groups. I think each group is going to have specific programs that they need to incorporate as far as training is concerned.

But again, I think we have started training. I think the workshop two weeks ago was the beginning of that training. I think we'll have a number of other workshops in the very near future. David mentioned risk management.

I think there are several other groups that are looking to have workshops. We may even decide to have some more stuff on dispute resolution because we feel we need to get information out there on the process very soon.

We have in dispute resolution too done a session with industry that was a smaller session than the workshop to begin to get input but to help them have a better understanding of what we were trying to accomplish.

I think, to answer your question, it has started. It doesn't have a specific working group, and I think that that will be developed very soon.

We're also talking about actually having a specific working group on communications as well because there are a lot of things, besides just actual training, that need to be better communicated as far as what we're doing.

DR. HUSSAIN: Just from a PAT perspective, I think that becomes an example for the overall initiative. You'll recall that we actually developed a curriculum and training and certification program for the PAT review and inspection team. So that is an example, but that is probably a higher level training that we are conducting right now. Last week we were at Purdue doing that. So in that sense, the training is happening from different angles. But as Helen said, I think the training group will

focus more on the starting level of training and then specialization and so forth. So you'll see bits and pieces that will come together soon.

DR. BOEHLERT: Other questions or comments from the committee? Gary?

DR. HOLLENBECK: I guess my perspective is it's a big job, and if initiatives have already been started, I think coordination of these initiatives would really be -- in my previous involvement with training, history has shown it to be a big job. It's an effort which requires coordination of groups that have been highlighted in your plan so far, and I think having a group step back and take the larger perspective would be something to give consideration to.

MS. WINKLE: I think we all appreciate that comment. We need to focus there and we realize that. Thank you.

DR. HUSSAIN: I remember working with you and the University of Maryland going through the SUPAC training and the challenges that we faced there. I think the challenges are great, but I think there's one aspect that we haven't discussed here which is having the right people to start with. That is another part of this initiative. We're trying to hire people with engineering and industrial pharmacy background also at the same time. So that's a

combination effort that will have to come also.

DR. BOEHLERT: Gary, did you have a response to Ajaz?

DR. HOLLENBECK: No, but at the risk of ruining my career, I would like to point out that the box that says "evaluation of the initiative" is chaired by the same person who's in charge of the entire steering committee.

(Laughter.)

DR. HOLLENBECK: I have the utmost respect for Dr. Woodcock, but I think there's an inherent conflict of interest there, and you might want to give that consideration as well.

MS. WINKLE: Thank you. What can I say without risking my career?

(Laughter.)

DR. BOEHLERT: Nozer, did you want to add something or have a question?

DR. SINGPURWALLA: Well, if there is time, I'd like to ask a question for clarification.

In one of your slides titled "Risk Management," you laid out in a very clear way what your goal is. It says to ensure systematic risk management approaches are applied to allocating resources, selecting sites and so on and so forth. That's very clear, but that is from the perspective of the FDA's operation. Is it my understanding

that this initiative also involves a reciprocal attitude towards what the industry itself does towards risk management?

If so, then the two risk management tasks are adversarial. What you would like industry to do would be, in a sense, adversarial to what industry would like to do. For example, industry would prefer that you don't come and do any inspections. You would like to go and do the inspection from your point of view. So there is an adversarial situation.

What I'd like to know is, does this initiative apply both to the FDA and to the industry or does it only apply to the FDA?

MS. WINKLE: I'm going to let David address that question.

DR. SINGPURWALLA: Is that clear? Is my question clear?

MR. HOROWITZ: Yes. I understand what you're getting.

I think the initiative really has two main pieces to it. One is changing FDA's behavior and approaches, but ultimately the goal is to change things that industry does. The two will work together.

So, more specifically, what Helen referred to there on the slide, those are the short-term goals of a

working group on risk management that is focusing on the internal piece as its first goal, and that doesn't mean that we're not interested in the broader approach to risk management. But that group is really focusing applying risk management concepts and principles to work planning of our own internal FDA work. That means what do we fund, where do we go, and what do we look at.

Now, that last question, what do we look at, I think actually has crossover potential. When we have greater process knowledge and greater understanding of the critical parameters and the variables that are predictive or associated with problems, that information I think is just as valuable, if not more valuable, to industry to focus its own resources and to improve and control its own quality.

So in many ways, when FDA figures out or has a better understanding of how to better focus its inspectional resources, that information will automatically be very useful to industry. First of all, they like to know what we're going to be looking at so they can get there and fix it before we ever find it. And second of all, I think it will be useful for them to focus their limited quality control resources on what we jointly can determine matters most.

DR. BOEHLERT: Any follow up?

DR. SINGPURWALLA: The only comment I'd like to make is that there may be some common ground, but there is also opportunity for an adversarial situation evolving because industry's attitude is to maximize utility. Your particular attitude is to maximize safety. So the two are kind of, by definition, adversarial unless industry wants to change its complete form of existence.

MR. HOROWITZ: Well, I agree with your basic point that there's a natural tension -- and there should be, frankly -- between the regulator and the regulated. But at the same time, it's in industry's interest to avoid problems with the FDA for a variety of economic and more public-spirited reasons. It's my view that when we are transparent about what we believe that matters most, that industry, assuming there's a sound scientific basis for those conclusions, will also benefit and be able to focus their limited quality resources on those activities, and in the end, they'll be better able to control their quality and improve the efficiency of their operation and ultimately be able to innovate more effectively.

DR. BOEHLERT: I think we have time for two more comments. Ajaz, then Efraim.

DR. HUSSAIN: Well, I think this is a very important point. In my presentation this afternoon, I want to build on that. That is, I think we can create a win-win

opportunity here, and science is what brings the win-win. And David alluded to this already. If you understand your processes and can justify that you have that level of understanding, then that becomes low risk. So there is an incentive for doing good science and understanding your processes. That I think would really create a win-win. For companies who do not, then our attention gets focused on them.

DR. SHEK: If I just may add some comments especially with regard to the quality. Yes, I think industry is a business, running as a business, but quality in the pharmaceutical business is extremely important and it's just good business. So this aspect is there. And it's true. The whole system is a check and balance system, and that's going back to human nature.

But maybe one thing to think about while we look at new -- and there are really fresh wins here -- and trying to change the approach is to look not only at the stick, but have some carrots because there you can achieve much more if you have some kind of specific benefits where both parties can realize that there is a win-win situation there. I think there is one initiative to have a development report there. If that can be as an example situated as a carrot instead of as a stick, I think we can achieve much more then.

DR. BOEHLERT: Unless you have one burning, brief comment, it's time for a break.

DR. DeLUCA: I just had one on the subject.

DR. BOEHLERT: Okay.

DR. DeLUCA: I would just inject a little humor before I ask this question along these lines. My tenure in academe is longer than it was in industry, but I've served on a number of USP and FDA committees. I guess a lot of times things come out when we talk about regulations. Colleagues in industry will say, we can't live with that. I usually interject, well, it seems like the patient can't live without the regulation.

A question I had was with the slide, "Changes Without Prior Approval." I guess this is something that this subcommittee is going to get involved with, these types of issues in much more detail. But I guess I just wondered what was the thought to allow post-approval manufacturing changes without FDA review and approval prior to implementation. Can anyone articulate on what types of manufacturing changes?

DR. HUSSAIN: Well, I think you will have several presentations tomorrow and this afternoon also on that.

But if we wish to have a continuous improvement model, innovation and change is necessary. And if change

requires a prior approval supplement and its associated long review times and the type of development information that needs to be submitted, then that becomes a hurdle for change or innovation and improvement. So I think we would like to create a flexible change model that is based on science, scientific understanding of the change, and thereby sort of reduce the prior approval supplement process for that.

MR. FAMULARE: It's a carrot.

DR. HUSSAIN: It's a carrot.

DR. BOEHLERT: It's time for a break. I'd like to thank all the committee members for very fruitful discussions this morning. There's food available here for the committee members. Please help yourselves, and we will begin promptly at 10:30. Thank you.

(Recess.)

DR. BOEHLERT: I think we have most of our members back again. I'd like to try to keep us on time, if we can, if at all possible.

Our next speaker is G.K. Raju, and I've asked him to just introduce himself. He missed the introductions this morning.

DR. RAJU: Thanks, Judy. My name is G.K. Raju, as you can see here. I'm the Executive Director of MIT's Pharmaceutical Manufacturing Initiative.

I was asked to give an academic perspective on the cGMPs. I'm going to give a personal perspective. It will be just my opinion, and because of the academic bent to this perspective, I'm not going to call it cGMPs. I'm going to call it manufacturing science, the means to cGMPs in the 21st century. Although I'm going to call it cGMPs, I'm not going to call "c" cGMPs, but GMPs because I'm going to challenge the word "c" in the cGMPs, and I'm going to say it's not current good manufacturing practice but future, great manufacturing practice that I really want to talk about.

(Laughter.)

DR. RAJU: Let's see if I can begin to shed some light on this.

This is an extension of a talk I gave on manufacturing science at the PQRI meeting that Ajaz asked me to present on, and I'm going to try to repeat a lot of that material and extend it to see if I can build a connectivity to our discussions from earlier this morning.

It sounds like an academic perspective. I'm going to start with a definition of some of the terminology. So let's see if I might start there. I'm not going to define cGMPs. I'm going to define manufacturing science because I think that's going to be the paradigm in which to decide whether we're good, current, or great.

When you're looking for a definition and you can't find one, you sometimes end up looking in the dictionary and you end up looking in a library. Somewhere out there somebody tried to do that before and documented it.

The first shot at trying to find a definition goes back in time to the very word "manufacturing" which, like many things in the world and many words in the world, is derived from Latin and comes from manus, which is hand, and factus, which is made, meaning made by hand. And if we were going to talk about great manufacturing practice for the 21st century, it sounded like I shouldn't go too far with that definition. It was a good place to start. We did do a lot of things by hand, but we can do a lot of other things by hand instead of pharmaceutical manufacturing.

So there was an opportunity to look for another definition, and a second one is the one below that says, manufacturing is the transformation of materials and information into goods, which are materials and information, for the satisfaction and maybe even delight of human needs. I like this definition a lot. It includes material and information, includes a transformation which is value addition, but connects to why we are doing all of this, which is to satisfy and delight human beings by

increasing the quality and quantity of human life. So that then is the definition I'll choose from the slide.

There was another word in this phrase, "manufacturing science," and I had to figure out the definition of science. So once again, I went off to the library. In this case I did find a lot of definitions and again ended up with the luxury of choosing the ones that I might use for this context.

Science can be viewed in many different ways, and here are some possible ways to describe it and define it. "A body of knowledge, body of facts or information, body of laws or principles, body of truths, verities or realities." Good stuff. "Skill, expertise, mastery, know-how." "Organized knowledge." "A means to solve problems." I would have loved that to be a means to capture opportunities because I don't believe there is anything such as a problem. But let's go with the definition from The Synonym Finder for now.

That then gave us some flexibility to decide which one to choose among them, and since this was the cGMP initiative, I thought I might choose the first one, and of course, the other ones below must apply.

We then have a definition of the word "manufacturing" and a definition of the word "science" and we've now got to figure out how to combine them into a

phrase we want to start talking about, called "manufacturing science."

When I first went to the library and looked for manufacturing science, the MIT library, there was no definition, but here on the next slide are the beginnings, I hope, of one version and one interpretation of a definition that we might choose to use. "A body of knowledge, laws, principles" -- that's from the science points -- "involved in the transformation of materials and information into goods for the satisfaction of human needs." That then is a definition.

A definition is a great place for academics, but doesn't always end up with something operational for people in the industry on the shop floor to use. We've got to start talking about building some connectivity from that definition into something that's tangible that we can change and enhance and measure performance around.

So let's let go and start describing the dimensions of manufacturing science so that we can connect it to some bigger system called manufacturing system, so we can figure out how we want it to be.

The dimensions of manufacturing science should now say, if that's the definition, what are its dimensions. One of the things I figured out very early on is that it's good to presume that we live in a Newtonian world where our

two dimensions are space and time. I haven't been able to figure out anything that Einstein has said really. I like the Star Trek, the Next Generation in terms of space and time in the next frontier, but for now, if we're talking about pharmaceutical manufacturing going beyond made by hand, I think it's okay to restrict ourselves to a space and dimension that are seemingly distinct. So that's the definition. Let's try to put some pictures around the space and time dimension.

Let's talk about extent of manufacturing science along the space dimension. You can then translate that into different levels that describe some set of discrete, not always easy to separate levels of manufacturing science in terms of this thing called knowledge, and there are different levels of knowledge.

Along the space dimension then, you can argue that you can start talking about different kinds of knowledge.

Descriptive knowledge. What did you do? Knowledge that says, I opened the top of the blender. I put in the excipients. I put in the active. Then I closed the top of the blender. Then I did this. This was my final reading on my certificate of analysis. And when the FDA comes in, they say, what did you do? You say, I lifted the top of my blender. I put in the active ingredient. I

put in the excipient and then I closed it and then I mixed it for 15 minutes. And here it is. I met specification. That is descriptive knowledge. That is meant to ensure that you meet safety and efficacy, which is did you meet specifications and describe what you did as part of doing that.

The descriptions of the how are about how you did different parts of your process. It's about connecting not just that blender but connecting it to all the unit operations before and after, which is the process knowledge, which brings the measurement and each of these steps together into a connectivity of how. How did you do this? I granulated. I blended. I dried. I compressed tableted capsules. That is your process flow diagram knowledge that in many cases is not part of your common knowledge that's shared across your organization, and that's the next level of knowledge that brings in the space and time dimension to your "what" knowledge.

In many ways, the focus of the cGMPs is about saying that you can do that, while the focus of the bottom level knowledge is to say that you're safe and efficacious and you satisfy the ultimate customer. Since the FDA cannot consume and test all of our products, they have to come down and look at our paper trail around our processes. That's the level of knowledge that they look at to figure

out if we have the level of knowledge that demonstrates safety and efficacy, which is the customer of our product, while in many ways we have a customer for our information and our paper product as well.

We then, over the life cycle of knowledge and space and time dimensions of knowledge, have the ability to either have known why we did things the way they are, which is why do we do this and this. We could do that in process development. You can learn that from the data during manufacturing, and that's the causal knowledge.

You can then figure out if you can get general classes of mechanisms, mechanistic knowledge. This is a first order reaction. This is a second order reaction. Here are the basic pieces of the models that I can build to get a mechanism that can begin to predict because a correlative knowledge in no way can predict. It can only interpolate that.

In the end, it's about going back to the basic first principles, and the basic first principles of saying this is my state of manufacturing science. This is my knowledge, and here this knowledge presumes that you've climbed the pyramid of knowledge, and that then is the space dimension of manufacturing science. So that's the space dimension.

What is the other dimension I should be showing

on my next slide? The one that we believe based on Isaac Newton is the time dimension that says we now have to decide where we want to be, where we can be, where we should be, where we could be on the space dimension over the course of the life cycle of each of our products, each of our processes, each of our organizations.

If you choose this to be the time when you actually submit your NDA and you first go into commercial manufacturing, ideally you could say I'm going to do all my learning and going up the pyramid of knowledge just before and after I go to the market because I have these large scale trials that I'm going to learn from a lot of data, a lot of experiences, and now climb the pyramid of knowledge. And that's my time profile along the space and time dimension of manufacturing science, and that's the learning by doing approach.

The good news there is you're learning about the product that actually goes into somebody's body. The good news also is that you're learning while you're actually making something and getting some money for it.

The other approach and obviously complementary approach is to do most of your learning before time, before you go to market, and you start at a much higher point. Maybe you start at level 5 which is the learning before doing.

Now, I want to make a clarification here. This does not mean that this company or this product does all that learning before time. In many cases, in most industries, academia, government, the industry in a social structure has put in place a set of principles that the industry can leverage to start at a very high point even as they start.

As you go by some of the comments that were brought up today, if society and academia haven't laid that foundation, it puts an overwhelming burden for the company for one product to suddenly climb this pyramid ahead or to do that in the case of this, when the basic principles of manufacturing science for pharmaceutical manufacturing have not been put in place.

Just for sake of completeness, that's the learning by doing. This is the learning before doing, which is often the lab scale and the pilot scale. But there are two other learnings before that. There's the learning through simulation and computers, which is even before that, and there's a learning by thinking and planning. So you can learn inside here by thinking and planning. You can learn in a computer. You can learn in your pilot and lab scale, or you can learn in your commercial environment. Each one is more and more expensive. Each one is closer and closer to "right first

time," and each one is more and more expensive as you go forward in time.

I'm going to start with just these two, the pilot scale, which you actually have to do a lot of design work, if you can. That's the academic piece of laying the foundation.

I want to emphasis this is a personal opinion slide. After having had a chance over the last 15 years to study pharmaceutical manufacturing in quite a deep way with a large number of organizations, it is my opinion that while there are differences in levels of manufacturing science in space and time across products and across companies and structures of the industry, it is very clear in my opinion that there is a big difference between where this manufacturing science is and where it can be, should be, and could be. And when I was at the PQRI meeting, I used this slide to say that the regulator, the FDA, the regulated, the industry, and academia all put together have a learning disability. And we need to find out how we can do more investments into pharmaceutical sciences ahead of time.

I'm not sure if this was said in my introduction. I had the great, good fortune of getting a Ph.D. in chemical engineering from MIT, and MIT claims, at least, that they invented chemical engineering many years

ago. If that is true -- and even if it isn't true -- I could tell you that in all of my curriculum I didn't learn anything about solids processing. Chemical engineering has gone into the liquids and the gases and the biotechs. There is nobody who works on pharmaceutical engineering or pharmaceutical sciences. If you want them to do it, they will throw you out. It is not one of their top priorities.

If you look at pharmacy schools, their focus has been more and more on the clinical side and more and more of the industrial pharmacy pieces are being lost, just when I'm saying that we have a learning disability. And many of these pharmacy schools do not train people to run plants at a large scale and a pilot scale, and as a result academia has very much mimicked the industry and the regulators' bigger structure of working together to move to this higher plane.

So there's reason for us to be here. There's a reason for having these academics and industry and regulators all in this room together because it is our purpose in life then to see and understand why we are not there, figure out if we should be there, and honestly within ourselves see if we can assist each other in making this leap in space and time upwards. The reasons can be business. It could be compliance. It could be cost. It could be cycle times. But in the end it's simply because

it's the right thing to do.

Those then are the different dimensions in space and time for manufacturing science. In the end I'm talking about manufacturing science. Let's just now connect that back to a manufacturing system, not because we want to forget the science, but we want to connect that science into something that we can start looking around and tailoring.

A manufacturing system -- and there is a definition here and there are many definitions of manufacturing system -- is a set of processes and systems bound by a common material and information flow. Notice, for the first time, when I put in manufacturing system rather than just science, there's a description of a process, and that process brings in a set of people that are bound by this same information and material flow. When I talked about manufacturing, I just drew a box around it. Now when I'm talking about a manufacturing system, I'm putting more description around the details of the box, around people and the system of space and time, the way they're connected to help us go from a set of inputs to a set of outputs. That then is a manufacturing system.

And if you look deeper at most of the manufacturing systems, particularly on the drug product formulation/fill finish side, this is a process flow

diagram of what many of these manufacturing systems look like.

So if this was the bigger manufacturing system and we want to figure out how we are doing, let's draw a box in space and time -- like I said, just like manufacturing science has a space and time dimension, so does the system -- and ask how are we doing with this manufacturing system. And we can measure how we're doing in terms of quality, time, cost, or safety.

Let's take a look at one of these process flow diagrams and ask what the manufacturing system looks like. The manufacturing system -- in this case their drug product, and it's shown in boxes all the drug substance in API side which is at least as important, if not more, but more difficult to show in a public forum like this. Here is a set of unit operations, one of the terminologies I learned in chemical engineering. Weighing, dry mix, wet granulation, a set of steps that I don't want to describe in further detail, drying, sieving, blending, and encapsulation.

If you look at this bigger system of making something, you will find that we have a lot of sequential unit operations, very little measurement of performance along the way, as a result, little or no feedback control along the way, and a huge burden of testing in this

pharmaceutical system at the beginning and end of this pharmaceutical manufacturing system.

If you then look at the tests at the back end of this process and you look at your C.F.R. 210 and 211, you will find that these tests map identically to those. We test exactly, to a large extent, the minimum that we need to test at the latest possible point in that process. Performance is made here and performance is tested here. If this is the set of causes and this is the set of effects, they are very, very, very far away in space and time, and that is okay if you are on level 4 and level 5 of the manufacturing science pyramid. That is not okay if you're in the level 1 and level 2 of the pyramid because then you have not designed the quality in and the testing is just for business reasons. You can even drop the test, but instead you are trying to, even though you don't really want to, test in quality.

This, particularly on the drug product side, is what a process flow diagram looks like. We have to figure out how we can make it look like this or even take out the tests by doing a lot of this level 4 and level 5 stuff ahead of time and figure out how we can go from level 2 to level 3 to level 4 to level 5 after, which is the learning and doing paradigm. So how do we go from here to there?

One of the benefits of being at MIT is the

Sloan Foundation, which funds a lot of work at the MIT Program on the Pharmaceutical Industry, has a number of industry centers where they look at textiles, semiconductors, and look at their evolution over time. And I've looked at the software industry and a couple of other industries and tried to map their evolution over time relative to a process flow diagram.

I've tried to capture those five levels of manufacturing science along these five pictures of a process that reflects that level of manufacturing science. Nobody exists in business here unless you're already at level 5 and you don't have to test. So let's not talk too much about level 1.

Level 2 is very much about a process that tests at the beginning and the end and very little in between. And if your level of variability justified that, that would be just fine, but in many cases this can be also mapped down to a level inherent internal variability or a sigma level. And this in ascending scale of sigma levels is in descending scales of variability or increasing levels of process understanding or increasing levels of manufacturing science.

What we'd like to do is to figure out what our process flow diagram should look like, measure what the critical variables are, but you've got to measure a lot

more before you figure out what's critical, then measure what's critical, analyze, understand, correlate causality, mechanisms, maybe close the control loop. And now we have a much more automated process, much more well-understood process. Now that we have it better understood, we don't necessarily have to test quality in. We might choose to do it for business reasons or liability reasons, but one day we may not.

The bottom line is manufacturing science described in those five levels of manufacturing knowledge has five levels of pictures in terms of what your process flow diagram could look like along these five levels.

And product by product, product class by product, processes by processes, our goal is to climb this pyramid either before doing or after doing, and hopefully both, because you can't do everything. You can't finish thinking before you do any doing, and you can't do all your doing without any thinking. Right? We can't separate thinking and doing to the extent that we have.

That is, we want to now climb that pyramid of manufacturing science and that's going to be reflected in our manufacturing system in the picture that we paint, and let's look at that manufacturing system now to figure out how we can go from here to there.

If you believe the personal opinion that we are

here, then we can now continue the rest of my slides to figure out how we can go there. If you don't, then Judy is going to get you during the discussion session and you can ask.

How do we get there? This is multi years of opinion about where we stand. Why and what are the implications now of this manufacturing science and manufacturing system and its implications?

What are the implications then of manufacturing science? Let's start with the FDA initiative, which is one of the reasons why we're here. We should be all talking about our own initiative rather than the FDA's initiative, but today we're talking about the FDA initiative which is the pharmaceutical cGMPs for the 21st century, a risk-based initiative.

So why was I talking about manufacturing science in the context of today's meeting which was about the FDA's cGMPs for the 21st century initiative? Because the first part of that initiative that Lester Crawford and Janet Woodcock and Mark McClellan and Ajaz Hussain and Helen Winkle list as the components of that initiative, the first thing they say -- maybe not the first thing they say. Sometimes the first thing they say is risk-based. But one of the four things they say is science-based. The other things they say are risk-based, modern quality management

techniques, and harmonization. And this is what the FDA calls the four pillars or the four pieces of their 21st century cGMP initiative.

But among them, I choose to only talk about this. Why is that relevant for the other four and why is that relevant to the initiative itself? Let's look at the science-based aspect of it, given this foundation.

First, if you agree that we're at the level 2 of our knowledge across the industry and our processes look like this, then that is going to show up in terms of large inventory levels; incomplete, delayed investigations because cause and effect are far apart; a low quality of life because we haven't measured and automated; and a disconnectivity between the making and the testing. Do we see that? If we see that, we've now to figure out what we might do about that.

One thing we might do about that is to see how we might leverage the FDA's PAT initiative, which by the way, I call the FDA PAT initiative, based on the web site of the FDA, to simply be this: simply an effort to facilitate introduction of new technologies to the manufacturing sector of the pharmaceutical industry. It's not about NIR. It's not about the technologies. It's simply about having a mechanism of communication between the regulator and the regulated, and that is most of its

potential benefit and most of its potential benefit can be described in terms of the consequences of us working together.

Why am I excited about that PAT initiative? It's because if you look at the cause of our performance, the process step itself, and the measurement of that performance, which is the actual test in the QC/QA lab, what we do in between is interrupt the process, secure a sample, hold a sample, document a sample, transfer a sample, batch a sample, prepare the test, then the actual test, test data collection, documentation, results, decision. Red are the human manual operations given by human beings and trees that are cut into paper. Those are the variable expensive operations. Those make it very difficult, even despite the test that's far away, to have a high enough signal-to-noise ratio to connect cause and effect that we need to do to climb the pyramid from level 2 to level 3 to level 4 to level 5. And we need to do that both in learning by doing and learning before doing.

What I like about this PAT initiative is it allows industry and the regulator to start talking about how we might bring in on-line technologies, the key word really being "on-line-able" rather than whether it's LIF or NIR or pattern recognition. It's not about the chemistry or physics about the test. It's about the paper and human

being of the test.

And the fact that we make most of our drug products in solids and test in liquids creates all of this red stuff. An ability to be able to test in solids is the on-line-able aspect that begins to connect cause and effect that lays the foundation, if we haven't already been there, to go from level 3 to level 4 to level 5. If you're already at level 5, chances are you already did that in development, and if you did so, you would see that in your inventory levels. The question is do you see that.

It's not about the technology. Most of this has been developed in other parts of the planet, other parts of this planet, and you can look at PAT technologies that can measure different aspects of this process, and you have many different ways of doing it. In this case I show about LIF technology that we discussed we've developed at MIT, but there are many other technologies that can be used to measure things that are inherently on-line-able connecting cause and effect. Not everything, but a lot more things than we've used so far and a lot more things that can give us a lot more value.

But it's not about measurement either. It's about using the measurements to figure out what measurement is important to figure out how you can analyze those important measurements to understand your processes better

so that you can now talk about designing quality in, which is the purpose of existence really, if you're doing pharmaceutical manufacturing, and was supposedly the purpose of the cGMP in 1978. Hopefully, it was about moving us up the pyramid. But where we ended up, the current state, is all of us looking very similar to each other.

In many ways I want to say that there shouldn't be too much of this "c" in cGMP. We want to all be different and at different levels of the pyramid and somewhere in the structure of academia, regulator, and regulated, we haven't had the right benefits and penalties and rewards for climbing that pyramid. And that's why all the stakeholders, or some of them, are here, to help us together as a society lay in a good cost-benefit tradeoff and a structure for it.

That was the reason why I talked about the science-based aspect in manufacturing science, but it connects to where we are. It connects back to the very purposes of cGMP.

But there were three other components listed in this initiative. Does it connect that? How can it not?

Let's start by agreeing that we make two products. A physical product for a patient for whom we greatly transform the quality and quantity of human life.

Taking a tablet is better than sitting in a hospital for two months. That is an increase in the quality of life. Taking a tablet beats dying for most. That's an increase in the quantity of life.

But we also, as part of 1978 cGMPs, have a responsibility for level 2 which has a reasonable level of understanding about how we went about doing that because the FDA, despite all the things that they don't have the ability to do, don't also have the ability to take all our tablets and consume them to see if they work fine.

So they have to look at our paper product and our information to figure out how well we are. Are we closer to level 2, which is very much that quality systems framework. It's very much about how do I look at the level 2 to figure out that you can do level 1 well.

Manufacturing science is about moving up this pyramid so that you can separate the safety and efficacy issues from the cGMP issues. Moving up this pyramid, as long as we are here in this pyramid, we -- I'm absolutely sure, 99.999 percent sure, that we make a safe and efficacious product. I do not believe this is a level 1 issue. We're talking about a level 2 issue because when you go back to the cGMPs of 1978, when we get approved with an NDA, we have a responsibility to have something already put in place on level 2.

And that is where it is not so clear whether the warning letters are talking about level 2 or level 1. In my opinion, I think we have a solid foundation across the industry in terms of safety and efficacy. I think that's a good thing for the FDA and academia and I think for industry.

The question then is about how we're going to do level 2. And level 2, once it's done, now actually begins to lay the foundation for us to climb the pyramid, which is really about understanding our processes not because the FDA says we should, but because we think we should or we know we should or because we could.

Really, this is about climbing the level of the pyramid so that we can make the FDA irrelevant. Just like the EPA doesn't have to show up in a plant too often, one day the FDA won't have to show up at our plants. And the only thing we can do to control it, the reward structure, is to climb this pyramid so that first, once we presume safety and efficacy, we want to presume good manufacturing practices, and the way to do that is to get to great manufacturing practices.

So how can manufacturing science not be about that risk? And if you look at each of those levels and their primary focus, the focus at the bottom is about conformance, conformance to product and process

requirements, which is the basic safety and efficacy argument.

The next level up is the focus on prevention and how you get there, which is failure, defects, complaints, and recalls, very much connected to the CA/PA systems and the quality systems. In many ways, when you have an effective process, that lays the foundation for an efficient process. You want to do the right things before you lay a foundation to do the right things well. You won't do them simultaneously, but you must lay a pyramid of effectiveness before you climb the pyramid of efficiency, otherwise you will collapse. That is, if you are here and you cut costs, the pyramid collapses. You want to lay the foundation of these two and then you have a highly profitable reward structure in terms of efficiency, cycle times, and costs.

This is about risk. Climbing up this pyramid, every part of this pyramid is a lower risk than the one below. This is the manufacturing science argument, but it is no different from the lower risk argument from a manufacturing point of view.

I would take this one argument further to say while we start with a customer and work at the risks and try to look at the bioequivalence and the equivalence between our products, our clinical trials, and our product

changes, there is so much of a lack of precision and accuracy in those connectivities from in vitro to in vivo, from bioequivalence to what is not equivalence, that we can only go so far with that minimal level 2 approach that centers around risk.

It's appropriate for the FDA to be calling it the risk-based approach, but if you really look at it, it's more appropriate for the industry and academia to be calling it the science-based approach because it's so difficult to connect from the product down into your process that you shouldn't necessarily have to start there to improve your process. Look at your process. Climb the pyramid. That's only going to make you stronger for all the risk issues coming on from the outside. In many ways, there should be an inside-out approach to risk management rather than just an outside-in approach, a process for its own sake approach, while in parallel to a product and its connectivity back to the patient approach because those are somewhat sticky data and very low signal-to-noise ratios. Those are signal-to-noise ratios of process performance that are basically appropriate for measuring level 1 and level 2, not appropriate for really being able to look at deeper issues of process understanding.

But really, this is the ability for you to automate. This is the ability for you to have a higher

quality of life. This is the ability to create resources so you can put it into prevention. And this really is the ability to ultimately, long term always guarantee that you meet specification.

The way to meet specifically is not look at what you did and whether you meet specification, but to focus on the capability to meet specification. So the higher and higher you are up the pyramid, the higher and higher is that capability, and the higher and higher is the ability to make the FDA irrelevant. Just like you want to bring your quality system into your process, in many ways you want to being some of the thought process of the FDA into your process so you don't need to have them disconnected to inspect you.

There is no difference from this side. It's just a matter of where they meet. In terms of the inside-out science-based approach and the outside-in risk-based approach, they are different sides of the same coin. This is the coin we have in our control, and I believe this is the coin that we should focus on within academia while we can focus on the outside-in as well.

What does this have to do with quality management techniques? Everything. If you look at quality management techniques along this manufacturing science pyramid and ask what is the focus of quality management,

you can go down to the focus at the bottom level on conformance, prevention, improved performance, superior value, and "right first time." And what really is that? It's about effectiveness and efficiency, performance excellence, and "right first time." It's about effectiveness in quality control systems. It's about effectiveness in quality assurance systems, which lay the foundation for the effective and efficient quality management systems, performance excellence, and doing things "right first time" even beyond just financial performance.

So in many ways this is modern quality management system and techniques. This is what Juran taught us and Deming taught us. That is, this is not about quality control. It's about connecting the quality control deep down into designing quality into your system.

Manufacturing science and modern quality systems. No difference. A difference in terminology and focus where you start, but very much integrated into the whole overall system.

You can talk about quality in terms of where you measure it and what is the time associated with addressing the cause for not being right and where you measure right. You can measure right outside in society by looking at whether you have a warning letter or consent

decree, and that's really far away between cause and effect, very, very far away, and really very expensive to start measuring your quality system there. This better not be your quality system. Manufacturing science says this better not be your quality system either.

Begin by laying your quality system to be some combination of this and this, which is your learning before doing and the level 3 of learning by doing. The manufacturing science is the inside-out approach to be able to enable this transformation to prevent you from going there.

I would argue that in a regulated industry, coming from here backwards is a very, very difficult thing to do. Although seemingly academic and esoteric, I believe that this initiative outside is a much higher probability of success initiative than one that focuses on incremental changes around there. It's about a bigger structure of manufacturing science in space and time.

What does this have to do with harmonization? I do not know very much about harmonization. I'm not sure how many people do. I certainly don't. But the bottom line says with all the new countries coming into EU, you might have different governments and different customers, and you now have to figure out how to harmonize around them. We just heard how difficult that is and why we might

need to postpone that for later.

An inside-out approach says you become independent of that government, that customer section. It's about doing things right. Once you do things right, you have now built a capability to harmonize, a capability to handle risk, and a capability to have designed the quality in "right first time." An inside approach makes now a common language between the FDA and the other agencies, we hope. Although I don't know much about harmonization, I believe that the foundations of manufacturing science very much lay the foundations for this harmonization which is very difficult to do with a government issue rather than connecting it back to process understanding.

We want to learn and move from a less learning before doing and even less learning by doing approach to a more learning before doing and more learning by doing approach. That is, during process development we want to be able to fail and explore the different boundaries of our processes instead of simply doing them similar to the way we did before and then having those few batches thrown out and then doing the same thing at the end, very much safe and efficacious. Everything in this is safe and efficacious. But we have not laid the foundation for us to ultimately hit the target. This is what a learning curve

should look like, which is a learning curve of that desired state, which is the learning curve of the current state.

So I'm hoping that all of us sitting together can then begin a conversation -- I would say continue a conversation -- that can enable this structural learning that can overcome this learning disability that I talked about.

That then I believe is the way that manufacturing science connects to the reason why we're here. But it's bigger than the FDA initiative. The FDA, I said, after level 2 should be irrelevant.

So the question is what is this bigger thing that we're trying to do that goes beyond level 2. And if you look at the pharmaceutical industry itself and look at the fact that all of us in our companies do research and development, manufacturing and marketing, and if you try to simplify this in some ways -- in fact, it really is oversimplified in this industry -- the R&D is the thinking organization. Manufacturing is the doing organization, and marketing is the talking organization. And we want to bring more talking and more thinking into manufacturing, and together as a structure of academia, industry, and regulated, we better create that structure.

And the fact that we haven't created that structure today puts the vice president of manufacturing in

a very difficult position. To me the hero is the vice president of manufacturing. When he gets his appointment letter, it says, welcome to the management team. You are now vice president of manufacturing of Merck or Pfizer or Glaxo.

But really, what's in the invisible ink in the appendix of their appointment letter and all the messages that that poor guy hears is, you are not as important as R&D and marketing. You are a cost. And really, at level 2 and level 1, you shouldn't be talking about costs. The guy before him says, the head of R&D says, don't be on a critical path. The guy after him says, just don't stock out. And the guy outside, the FDA says, now, you told me you're going to do it this way. Now, you better do it the same way for the next 12 years.

Clear definitions of failure, dysfunctional, almost incomplete, may be missing definitions of success. And if you have only a definition of failure and no definition of success, what will your risk-reward tradeoff be? If the only thing you can do is fail, what is the only thing you will do? And if the only thing you can do is fail, how much risk will you take? Little or no, and that's not a good thing for manufacturing science. That's not good for the vice president of manufacturing. It's not good for the company. That's not good for society.

So it's about those four pieces of the FDA's cGMP initiative. It's about putting pharmaceutical manufacturing right to its rightful place in the overall organization and the overall academic and social structure. Not everybody is going to make it up that pyramid. So finally, just like big, small, and medium pharmaceutical companies compete by their ability to research and market, they are now, I hope, at the end of all of this, two years and beyond, going to be able to compete and be different in how they do manufacturing.

That is the business proposition that must exist for us to capture this, enable this and encourage them. And that's the point that Efraim made about putting the rewards in place for us to enable climbing up this pyramid. That is about process understanding. That is about decreased variability, and of course, that is about lower costs. But we're not going to get to that lower costs unless we get to this level of the pyramid, and we have got to help each other climb that level of the pyramid.

That is also about a change in the industry structure in terms of what the FDA should do and what it is able to do, and now if we climb that pyramid, the FDA does not need to come into our plants as often as they do because you have now climbed the pyramid and communicated

to them. And that's the foundation for asking for a reward tradeoff from them, and the inside-out approach says, let's focus on what we can do in terms of climbing the pyramid and describing the data and knowledge and framework to do that, and then let's go to the FDA and make a deal for saying that they're not going to come inside our plants once we climb above level 2.

That then is manufacturing science. I talked to you about the definition of manufacturing science. I then talked to you about the dimensions of this manufacturing science. I talked about where the manufacturing system is today and where it could be tomorrow. I talked about a path from here today and talked about the huge implications of being able to, together, go from here to there in terms of science, in terms of risk, in terms of modern quality management, maybe even harmonization, but really about business and really about doing the right thing.

I would, again, make the last point that one day I hope it will be the science-based initiative for the 21st century rather than risk-based, and that should be what everybody else does in academia and industry, not necessarily what the FDA does because their focus is to ensure safety and efficacy.

I am ready to take some questions.

DR. BOEHLERT: We have time for questions because we only have one speaker in the next session. So fire away.

DR. SINGPURWALLA: I come from a very different culture than you come from. So a lot of my questions will reflect that particular side of the culture.

You raised in my mind a very important notion that perhaps is very useful for this particular group, and that has to do with the five levels of -- I believe they're due to Crosby.

DR. RAJU: Sorry?

DR. SINGPURWALLA: The five levels that you mentioned.

DR. RAJU: Different people have different kinds of knowledges. Crosby has done a lot of the quality management, together with Juran.

DR. SINGPURWALLA: Now, I had the pleasure of working Walt Humphrey at the Software Engineering Institute where what they did is they took a software house and placed it in one of these five levels that you mentioned somewhere along the line. The motivation for that was that the Department of Defense would give software development contracts based on the level at which the particular organization belonged. So there was a motivation for these organizations to get themselves rated.

The process of rating involved a long series of questions. It was completely ad hoc. Then at the end of that process, a particular organization -- just pick a name -- software house was placed in category 1, 2, 3, 4, or 5. Nobody achieved category 5. Maybe just one organization achieved. Most of them were at category 2.

Now, the complaint I heard from the other side is that any process that places an organization in one of these categories with any sense of definitiveness should be flawed. In other words, they could only place them in these categories with a certain probability, and calculating that particular probability was not an easy task.

So the first part that comes to my mind is could a similar system be developed by the FDA. The software engineering system was called the "capability maturity model." And I'm just wondering or at least throwing open the idea that one may consider some kind of a parallel scheme, recognizing that these schemes have a lot of obstacles and objections associated with them. So that's the thought occurred to me.

Now, the second thought that occurred to me comes from my academic cultural background. You constantly used the word cause and effect. Of course, that's a very deep philosophical question which plagued Newton and

others, and it's a very difficult thing to essentially come up with a precise cause and effect relationship.

And the other point is you called science-based manufacturing and you contrasted it with risk-based manufacturing or you wanted the word "risk-based" to be removed and it be called science-based manufacturing. Now, my thought goes back what is the scientific method, and basically it boils down to this, that if you cannot quantify, you cannot talk about it, and if you cannot quantify, you cannot use the logical method. So quantification is absolutely a fundamental step to be able to invoke the scientific method. A lot of what you said is not quantifiable. So I would challenge that it be called scientific.

Now, recognize I come from a different culture. So I want to stop at that.

DR. RAJU: Sure. Let me try to take all the three points in sequence.

Just to kind of connect back to the comments, going back 10 years now, a little bit later than 1988, the 1980s now, Carnegie Mellon University developed the CMM model which is for software, which is the capability maturity model, which was referred to here. Dr. Humphrey and a whole bunch of people have developed a framework of rating software companies. It started off with a bunch of

failures in the defense industry, the fact that they had to allocate contracts to different people to put software into something that takes off, and how would you base your decision about who you're going to do it with. That resulted in Carnegie Mellon, together with the Department of Defense I believe at that time and a whole bunch of software companies that resulted from it -- and I think benefitted greatly from it -- in rating things in terms of level 1, level 2, and level 3. And there are many books around written on the capability maturity model, and that's now been expanded into a people maturity model and other dimensions.

I fundamentally believe that that was a very successful approach. Today there are 20 or 30 software companies at level 5 just in India just in a couple of cities. When you're at a distance far away and you want to get a contract from a big person who doesn't have the ability to inspect, you have to lay in a foundation of describing your level of knowledge. And a company that's very small and doesn't have to be inspected has now created that foundation to be able to rate its ability to make software.

I believe the general principles of that are quite applicable in the case of pharmaceuticals. I would actually argue that in the case of software, it's

inherently at least as difficult to measure as pharmaceuticals. I think that pharmaceuticals are at least as inherently capable of being measured -- this is my opinion -- in terms of ability to measure because we're talking about defined physics and chemistry. Macro scale doesn't necessarily mean the case. Human beings interacting with it and many of those pictures that you saw connect back to the software capability model as well. So that's the first framework.

I think a lot of it applies and I believe strongly in it. I'm not so sure that the FDA should be the one that drives the intellectual content of that quantification and levels. Similar to Carnegie Mellon, I think somebody similar to that and a neutral party has to define some of the pieces around it. I think the process capability measurements that come from the whole TQM society nicely fit into quantifying different levels, and that's a nice thought process in terms of CPKs and CP to measure capabilities for many different aspects of effectiveness and efficiency.

So a lot of foundation of quantifiability is already done. There are parallels in other industries that we could grab, but I'm not sure that the regulator should do that. I think industry and academia should develop the foundation just like the past. The FDA should probably

connect back with the Department of Justice to connect with some learnings across it and then be the ultimate decider of whether to use it or not, of course. Of course, there are many other extensions of it.

So let me go to the second question. I agree. There is no such thing as a cause. There only different levels of causes. Why am I tall? What is the cause? Because my dad was tall? He wasn't. So I've got to go down to different levels of causes, and you want to be able to ask the first, second, or third question. Usually in this whole total quality management thought process you say, let's ask why six times, and by the time you get to the fifth or sixth time, you've gotten close to a cause. But there is no such thing.

If you go back and ask a question, what is the cause of Brownian motion, you might say just molecules that vibrate. But sometime deep down inside, if you go further, you might be able to find a cause. So at every point, there's a level of granularity of cause and effect based on the purpose of that problem solving process. The cause at each level of the pyramid is a different level of thinking.

The third point about quantifiable. I feel one of the difficulties about why they used this whole capability maturity model in software was because it was so difficult to define those processes. So it began to define

the processes and do the quantifiability. It's actually quite difficult to quantify, in some aspects, software. I think many of those are applicable here. I think that whole measurement aspect of performance beautifully maps onto the PAT initiative which is at level 2 and level 3 which is about measuring relevant process and product performance for the sake of process understanding. It may be connected to safety and efficacy, but it's more level 3, level 4, level 5 measurement for the sake of process understanding.

So that would be my three or four thoughts on that.

DR. BOEHLERT: Efraim, did you have a comment?

DR. SHEK: Yes. G.K., I'd like to refer to the term of the science, and let me start with a question. Why isn't MIT spending time understanding the engineering of powders and mixing and granulation and so on?

The reason I'm asking the question is because I am somehow concerned that we are going to miss the target here. So when we use PAT, basically what you have shown we do a lot of measurements. And that's right. It's the first step. I would assume we need that understanding. What I didn't hear is where is the next step we are going to understand in other processes. Because a new dimension there -- and I think it's important. Time is a composite

of many impacts. It's not just the seconds, the hours. Things are changing. You have a scale-up, you change equipment you are using, changes in the drug substance quality. There are changes in the excipients, and that happens at a time. So time is not just one measurement.

We can do all the measurement we want. If we don't still understand, we don't have the knowledge base -- and that's why I'm referring to MIT and other people in academia. Something has to be done to understand more the principles and knowing on a small scale how it's going to behave in a large scale because that's really the big timing impact. I would like to see something is happening there.

DR. RAJU: Sure. Let me sort of answer both those comments, although not questions, in some personal way at least.

Why do universities fund something? Is it because somebody pays for it? Usually they fund a set of important problems, a set of important applications, among the different things that they want to do. If you look at where they get their money from, they get the money from industry or they get the money from government. Those are the two big sources. There could be other ways. There could be foundations.

Go back into industry and you ask the CEO of

manufacturing to put some money, where would he put the money? Talk about Novartis coming down next to MIT, putting all their money in MIT to be next to MIT. It's about new drugs. That's the CEO's tradeoff of where to put his money.

I've tried to do this personally, apply for funding for pharmaceutical manufacturing from the National Institute Standards or some part of the government. Where do they put their money? They put money on bioinformatics or genomics. Those are the better tradeoffs for them. Those are the better tradeoffs for the pharmaceutical company. There's a bigger social structure that says, that is where the biggest bang for the buck is, given the time frame that I have of a few years.

The consequence of that, yes, it may be justified for this pharmaceutical manufacturing and the science around it to be a lower priority than genomics and bioinformatics and for it to be a lower priority than R&D and marketing. So that takes care of the relative priorities. But despite its seemingly lower priority, not having done something about it for a long enough time creates a lack of missing knowledge that everybody deals the consequences with.

Now let's connect to the next point that you made. If you want to now generate this knowledge, your

costs, to a large extent, come from the material and the scale of your operations. If knowledge is about generating information per unit of material, then the way to do that is at the small scale.

And so it is exactly your point. The way to get that knowledge is to go back to the small scale where you can get a lot more information per unit of material. The way you do that is by choosing the right measurements that gives you the right data that you analyze and then you understand it and you create the knowledge. And so I like the measurement piece.

However, there's a whole other piece that says, we don't want to take all of these steps and go to the small scale and start understanding and measuring. We're just not going to do drug product manufacturing like this anymore, which is a whole new set of making drug products, different kinds of drug delivery technologies. So you either lay the foundation or you simply make it unnecessary to do things. Now if you focus on drug delivery technologies, a lot of research and funding has been put there. It's higher on the priority list.

So there's a reinforcing dysfunctionality, but there's a reason for that. It's the reason that it lives in a bigger society where many of us sitting around the table, even if we weren't in manufacturing, would have made

the same decisions.

I think a nice outcome of all of this is for the FDA, now as a regulatory industry very much focused on the pharmaceutical industry and not necessarily on long-term bioinformatics and human genomics yet, to make the case for a special focus -- either the FDA or the government and academia -- to this because it's the right thing to do anyway, and for the FDA to say we have been working with this. We think there needs to be a structural connection back with the government. Even though this is a lower priority than genomics, this is still a higher priority than not doing it.

And I think the FDA and two or three leading universities have laid the foundation to do that. I will maybe let Ajaz comment on that further. I'm familiar with most of them, but probably Ajaz is itching to say something there.

DR. HUSSAIN: No. I'll pick it up later on.

DR. RAJU: Okay.

DR. BOEHLERT: Tom?

DR. LAYLOFF: I was going to comment a little bit about the manufacture of dosage forms because from the outset it's trivial because you know all the components that you're putting in very accurately and you can calculate out the average properties of the final forms,

but in solids the behavior of heterogeneous solid mixtures is very difficult, I think, from an engineering point of view, and solutions and gases are very easy. So they are trivial to deal with. But at the outset, the formulation is trivial, but the process is very poorly defined because of the heterogeneity of the system. So it's very difficult. I'm not sure it's soluble. I think you're stuck with PAT of defining endpoints rather than understanding what's actually happening.

DR. RAJU: So you believe that we're stuck with that at the beginning and the end and we can't do anything in between.

DR. LAYLOFF: I think you can define endpoints in the heterogeneous system, but as far as understanding how it gets there, I'm not sure you can do that.

DR. BOEHLERT: Other questions, comments? Pat?

DR. DeLUCA: Were you going to comment on that?

DR. RAJU: It's an opinion that might be valid if you've already defined and understood your process. But I think if you haven't, then having the cause and effect so different from each other makes a huge price to pay for society. The FDA has to go in everywhere. The industry has to be so manual. Automation becomes nonexistent. We end up becoming documenters instead of learners, and we don't evolve to the higher quality of life in making. The

question is, is it unsatisfactory? We agree. Is it a difficult problem? We agree, otherwise it would have been done. Should it be attacked now and addressed? I think so and that's why we're here I think.

DR. HUSSAIN: Just to add to what Tom mentioned, I think it's doable, but I think he's also right that the pragmatic solution is endpoint at this time. And the primary reason for that is the task to get to what we would like to is humongous and the source of that challenge comes from our materials not being characterized and understood from a physical sense to a large degree. But I think getting an endpoint is a means to managing variability, and I think it would be a leg up, a significant step in the right direction than what we do as use time as a control right now.

DR. RAJU: The key is it's got to be voluntary because it's safe and efficacious in level 2, and companies can choose whether to climb the pyramid. That's fine. Whether it's difficult or not is their own decision. However, there is a bigger structural foundation that's missing that's not about the company's decision, about the fact that maybe we all have to put a structure together to lay the foundation for them to make that decision easier.

DR. LAYLOFF: Then also I would say that controlling a process is different from understanding it.

You don't have to understand everything to control it repeatedly. Automation is repeatably doing things. You don't have to understand each step.

DR. RAJU: There are different levels of understanding, and at level 3 and level 4, when you can get a set of correlations that have some meaning, you can begin to lay the foundation for an automatic control around certain boundaries, but you'll have instability outside those boundaries if you don't know the first principles.

DR. LAYLOFF: And there may be some time when we will learn how tall you are, but we can measure it very easily.

(Laughter.)

DR. DeLUCA: I really enjoyed the presentation. I think it was well done. You put a lot of time in on it.

Before I make a comment, I recall back in the 1970s FDA had a symposium on total product quality management. I participated in that, and there's a pink document, monograph that was actually published. I think probably a couple of printings went into that. But my part in it was to look at the case studies with regard to self-inspection, self-evaluation in the industry. So I had contacts in the industry -- this is after I went to academe -- and was able to do this.

One of the things I emphasized I guess in my

talk -- it was a little bit spiritual too -- was doing things right the first time, which you have emphasized here.

As you move up that pyramid -- and you positioned just nicely where FDA was at the second level, and I think that's where we stop is at that second level. But there's a deterrent from going further up that pyramid, and the one is that before the product is introduced now, I think there's the mentality of high throughput screening and wanting to get there as quickly as possible. So many times it's getting the product and if it's working, not really going into why and getting up that pyramid.

The other one is afterwards there's a deterrent of don't change anything. This is the way it is, especially with generics and that. When you come out with something, you don't want to change it because that's the way it was, and so you don't make it better. I think there's a hesitancy to really stress the process, take the time to have a failure. Like I always say, in baseball, if you've got a base runner and he tried 10 times to steal bases and he stole them 10 times, well, it doesn't mean hasn't tried hard enough. He should have tried 100. It's better to maybe get caught a few times to show that you really tried.

As an example, I'm involved with a process.

There's a product on the market. It's freeze-dried. It's been on the market for about 20 years, and it's like a five-day cycle. Well, the company wants to put a generic out, and they came to me because I've done some experimentation with freeze-drying. I looked at it and I said, well, this cycle should not be five days and there are ways to make it shorter by stressing the product.

I like your slide you use with the target there. The idea was to try to fail, so you stress the process knowing that you're going to fail sometimes, but then you can hit that bull's eye.

But the point here is that there's a deterrent because the company is saying, this is the process and we don't want to change it because then how will you file for an abbreviated NDA.

Or to be able to add, let's say, a mass transfer accelerator to the product to shorten the drying cycle. Now, the mass transfer accelerator is going to be removed from the product when you're finished, but it means adding something, a volatile substance, to be able to dry faster. And that's a no-no. Now, I think here in the United States probably the FDA would accept something like that, but whether the European market would accept it -- they'd come right back and say, well, the Germans wouldn't accept this.

So these are, I think, deterrents that we face. It's real life. So I commend you. I think that's great. I like the idea of moving up that pyramid, but it seems like there's a lot of deterrence. I think the climate is such that there's deterrence for this.

DR. RAJU: Patrick, it sounded like there were two classes of deterrence. The first one is the learning before doing where you're trying to make a business tradeoff of don't be on the critical path. Why should I take a risk that might slow me down? And there are two pieces to that.

I'm not sure what the FDA has to do with that or can really help with that. However, they do have a role in educating themselves earlier in the process about possible technologies and increasing the probability of a new technology being accepted and not being on the critical path. So that would be one way the FDA has a role.

But really this is a bigger issue about what is the relative importance of products versus processes. As you say, the business decision usually prevents too much of learning before doing. Over the last 10 years, I've seen a trend that seems to be headed even more in that direction. If you look at the head of manufacturing, he actually is trying to figure out the perceptions of making changes and the learning by doing. But the learning before doing

piece, especially on the drug product side, has largely been kind of in the pharmaceutical sciences group within the R&D groups. Since the process is so much lower down on the totem pole, relative to the product in those organizations, every year over the last 10 years that group is getting smaller and smaller and smaller. So it's getting even more true from a science side, and that's going to further complicate situations in terms of the learning before doing.

That kind of a business paradigm -- maybe moving pharmaceutical sciences into manufacturing would be one business organizational issue, but there's a tradeoff of product versus process. There's an education process from the FDA saying we are going to help you earlier on increase the probability of the success, and then there's another kind of technology and thought process that says, actually process innovation is going to get you there faster rather than slower. So there's a nice paradigm there that might help.

On the learning by doing paradigm, I think it's very much about building in a framework that says you can makes changes and here's how you can make. It's about taking the SUPAC kind of a document, which is a level 1 to level 2 kind of document, and having an equivalent for level 2 and level 3 and building in more information and

structure into it and having a communication, just like you did on PAT, about process understanding and evolution up that pyramid. And that needs I think perception or real communication and maybe a guidance document and maybe some basic rethinking of the word "c" in cGMP on the second piece. Both of them I think need some help.

DR. BOEHLERT: I think I'd like to cut the discussion at this point in time because we have one more speaker before lunch. Thank you, G.K.

DR. RAJU: Thanks.

DR. BOEHLERT: The speaker is Colin Gardner. This is now the open public hearing part of the agenda.

DR. GARDNER: Thank you very much to the organizers for giving me some time to present this morning. In the interest of full disclosure, I have to tell you who I am and what I represent. My name is Colin Gardner. I'm currently the chief scientific officer at Transform Pharmaceuticals. It's a high throughput technology company in Lexington, Massachusetts focused on finding new methods to look at the form and formulations of compounds.

Formerly I was the Vice President of Global Pharmaceutics R&D at Merck, and I was there for 19 years.

So what I'm going to present today are my own thoughts, just like G.K. I'm not representing Transform necessarily or Merck. But we also have another thing in

common. We both have got a heritage from MIT chemical engineering. So maybe what we've got to say is very similar.

The reason I'm here today actually is because Ajaz asked me to come down here. I was the former representative on the PQRI product development group. During the discussions of that group, the subject of SUPAC came up on a number of occasions, and I coined the phrase, "create your own SUPAC," because I felt the SUPAC that was defined back in the early '90s really was a very, very narrow document and really bore no resemblance to what was really done in developing a product. So we came up with that concept, but it didn't catch on very well I think.

So I made a presentation probably six years ago at a workshop, and I've pulled a few slides from that to use as a description of where I think we may be going.

So let's look at the facts then. Drugs are really materials and I think we tend to forget that. The rest of the world thinks about materials, but we tend to think of them only as organic drugs.

Pharmaceutical production processes are a series of unit operations, as G.K. just told us, and these operations are governed by exactly the same chemical engineering principles as any other operation in the manufacturing industry, whether it's in the chemical

industry or the software industry or whatever. The problem is that we really need to treat them that way, and I don't think we've done that in the past.

So if we look at a historical time line here of things that have changed at the FDA and relationships with industry over the last decade-and-a-half, first of all, we had preapproval inspections. Then we had the SUPAC document. Then we had the site-specific stability issue that came and went. We had PQRI and now we've got comparability protocols. G.K. has already touched on issues associated with a number of those. So I'll just concentrate on SUPAC and comparability protocols because I think they're related.

So if you go back to the early '90s, in pharmaceutical research there was a publication on where SUPAC was coming from. It said for years the agency has had difficulty developing a regulatory policy based on solid pharmaceutical principles for scaling up solid oral dosage form batches. And we've heard several people say that it's very difficult to do because you're dealing with solids and powders. You're not dealing with liquids. And that's certainly true.

The published scientific literature does not presently provide a sufficiently rich source of data to enable such regulatory policy formation.

They went on to say, additionally, the process should be controlled by employment of a validation protocol which defines the critical parameters and also establishes acceptance criteria for the granulation or blend which may include sieve analysis, flow, density, uniformity, compressibility, and moisture. These, I think, are what someone referred to as controlling the process, but this isn't understanding the process because all these are just phenomenological measurements. They're not fundamental process parameters that can be used to model and predict process parameters as the conditions change. And the conditions do change. The excipients change over time or your drug product changes a little bit over time, and it can dramatically affect your process. If you don't understand your process and the key critical parameters that control it, you will never be able to react to those changes.

So let's look at the SUPAC guidelines. This is just pulling one section of it. For composition, if changes are defined as minor or major, they're purely arbitrary. So you can change 5 percent in a filler and you don't have to do anything. If there's a change of more than 20 percent in the particle size, you have to change something. If there's a 20 percent change in the volume of the granulating fluid, you have to change something.

Where are the data to support these changes? And would you really expect them to be valid or to be the same for every single process or every single formulation? And I think the answer is a resounding no.

So here's another quote. "It's been decades since the chemical engineering discipline made the transition from a highly descriptive framework of distinct unit operations and processes to a generalized body knowledge based on interlocking fundamentals, transport phenomena, thermodynamics, kinetics, and chemistry. These fundamentals have been quantitatively developed so as to create powerful predictive tools that permit us to apply know-how acquired in one context to any other, as well as to deal with the broadest range of natural phenomena." And that is what we have to do when we design a pharmaceutical process. This came from Carlos Rosas who was formerly head of chemical engineering R&D and then manufacturing at Merck.

So a different look at SUPAC, and I'm going to talk here about the pharmaceutical product processing because, as we've already heard, when you're talking about the API processing, 95 percent of the time you're in solution. And we know how to control solutions and we can monitor solutions. But two parts of the API production which are usually not in the liquid state are the final

crystallization step and the control of particle size, and these are the things that process chemists least like to do. They love to design a process that's very efficient, that produces very few intermediates and also has very few impurities, but they don't really like to work on these last few parts.

But what we have to do is completely characterize the API to select appropriate manufacturing processes based on what that API is and the particular form we've chosen to develop, characterize each unit operation, and then establish scale-up, tech transfer and validation criteria.

Unfortunately, the way in which a lot of the industry works is not by doing that at their small scale, as G.K. said, but by very quickly getting into manufacturing, making the clinical batches in manufacturing, making all the phase III clinical supplies there, tweaking the process, filing that process, and then the FDA comes in and says, where did you make your phase III clinical supplies? Made them in manufacturing. Where are you going to make your final product? Manufacturing. Click. So we don't really need to worry. It's the same place. It's the same process.

But do people really understand that process and what happens if something subsequently changes? And

the answer is no because they didn't do the fundamentals.

So these activities would alleviate many of the production problems that were evident in the industry, and we've seen many, many companies get into significant trouble because they had GMP issues on scale-up.

And this isn't even envisioned in the current generalized SUPAC guidelines. So that's why I believe we should create our own SUPAC.

So let me just compare that with comparability protocols. The FDA guidelines came out, I think, in February, and it's really similar in concept to "create your own SUPAC." But it will really only be successful if pharmaceutical processes are adequately developed and the influence of fundamental process parameters are understood and then used to define the protocols for scale-up, for technology transfer, and raw material formulation, and process changes because all of these will occur at some time in the lifetime of the product.

So I just wanted to concentrate on a couple of areas here. There's a whole range of things that you do at various stages from candidate selection through form selection, composition and process, process development, scale-up, tech transfer, and then post-approval changes. And you really can't separate these three because form selection, the composition and process that you use to

develop that form, and the process development will all be intimately tied together. So you don't just select the form and then select a composition. Someone said it was a very simple job to fix the composition. It's really not. It's very intimately tied into the process.

So I'm going to give you an example of form selection and I'm going to give you some examples that we had from Merck. These aren't outstanding examples. They're fairly simple examples of how you can control your process.

So I hate to make Abbott the poster child here, but they were the only ones, unfortunately, that were caught in the marketplace. I think almost every pharmaceutical company, when you ask them, will tell you that they've had a new polymorph appear at some point in their history of development of a particular compound. Abbott was in the unfortunate situation that it not only appeared after they were on the market, but it appeared in a product that was very, very highly visible because it was an HIV protease inhibitor for AIDS.

They developed a compound in 1992, launched a capsule in 1996, and in 1988 they started failing dissolution specs, and it was virtually tied down that this was a new polymorph with lower solubility. The product was then promptly pulled from the market in that form and they

put in a massive effort to reformulate that, and it was back on the market again in its form two in 1999.

So one could ask yourself -- and many of us have asked this question -- how could we not find one of these polymorphs during development?

So nowadays there are high throughput technologies, and I'm speaking for Transform, but there are many other companies and within large companies and also other companies that are doing this today, that are using parallel processing of thousands of crystallizations to be able to find conditions to explore that entire space in terms of forms, salt forms, hydrates, polymorphs. Then you get a very comprehensive discovery of solid forms which then gives you more informed and better choices, which then eventually can lead to better products.

So we selected ritonavir, and we said, okay, what would we have done with ritonavir if we had that compound. So here's the time line. Abbott started with form one. Later they found form two. We took this material and we put it through a high throughput screen with 2,000 crystallization experiments using 2 grams of compound, 32 different combinations of solvents, and we found five forms. We found the two original forms and three other forms. These are less thermodynamically stable so that this is still the most thermodynamically stable

form, and so it's the right one to have on the market. But this took only six weeks to find. And this publication, by the way, is in Proceedings of the National Academy of Science this year. So it shows you that by being able to use these kinds of techniques, you can learn. You can explore the whole space with a very small amount of time, and this took six weeks.

Let me talk about processes now. This is where I disagree with the idea that you can control a process without understanding it.

If you explore your process at a small scale, you can find out where the process is unstable and where the process is stable. Then you can set, as a result of that, some parameters which will allow you to track the drift of that process, and so you know where it's going before it falls off the edge of the cliff onto the unstable region.

So let me give you one example. Someone spoke earlier about a lyophilization process. The idea here was by putting a residual gas analyzer onto the end of a lyo chamber, you can monitor this in development and you can determine your conditions. Then you can use those same parameters then in manufacturing. Then you can put a residual gas analyzer on there. The ability to do this -- the manufacturing division -- and I'm talking here about

the head of manufacturing had to decide to do this. And this was no simple choice because know, when the FDA comes in, they're going to see this information. And this is not a filed specification. This is a process control. So the fear is that the FDA will see a change in this process control, and they'll say, what's going on here?

So it really means that in development you have to understand the process. You have to understand the range that produces a satisfactory product and you set those ranges so that in manufacturing, you can control it within those ranges. You monitor for trends, and when it starts to trend out of the normal range, then you know something is happening. You challenge your process, find out what's wrong with it, and get it back under control. And I'll come back to that point later because I think it's important.

The second one. Very often in the industry in the past -- and I know this is changing, but people would simply take their powders. They would dry mix them and then they would add granulating fluid, and then they would mix for a certain time. And so the NDA would read, mix for 10 minutes plus or minus 2 minutes or something like that.

But in fact, a very simple thing you can do is to do granulation endpoints. So you can measure the power in the mixer and you can normalize that as a function of

the amount of water, and you can do this at different scales. So here's comparing a 65 liter with a 10 liter, and you can see that basically these two curves totally overlap. Then you can go to the next scale and you can compare a 65 to a 250 liter, and again they overlap. So now you control to that endpoint. You don't control by time. You don't control by volume of granulating fluid. You control to get to the same conditions that produces the same product.

A third example is a controlled-release formulation. And this is a pretty complex formulation. It consists of the drug dispersed in a water soluble polymer, which is then overcoated and then the tablet coating is drilled by a laser to produce many, many holes in the surface. When this goes into an aqueous environment, the water will penetrate through the film, cause the polymer to swell, and basically you get spaghetti noodles extruded from this, carrying the drug with it.

So if you're going to develop a process like this, you better understand all the critical parameters. So what happens if you change either the polymer or the neutralizing agent that's in here to control the conditions of swelling? You modify the amounts of each of those and you look at how it affects the drug release. So now you know even if you change within plus or minus 10 percent,

you're not going to change the overall performance of the tablet.

Likewise, in terms of the laser drilling process, you can change the pulse width and the power at constant energy, and you get essentially the same release rate. So now you can control the drilling process by the energy per hole as a process control.

Likewise, you can compare the hole size with the release rate and now you have the same curve regardless of the coat thickness that you have on the tablet.

And finally, you can look at the effect of the number of holes, at any one size of hole that's been drilled, and you can see that if you have only 20 holes in the tablet, you get this release rate, and this increases as a function of the number of holes.

If you want a robust process, then you better be up here because if you missed a couple of holes down here, you would change the delivery rate quite considerably. If you're up here and you miss a couple of holes, it doesn't make any difference.

Likewise, if you fix the number of holes and you now look at the hole size, the same applies. If you're down at this low end, if the laser starts to change in its energy as a function of time, then you're going to start changing the hole size and you could change the release

rate. If you're up here, then you could have much larger variability of the laser power and it still will give you the same product.

So I hope that I've shown you that, in fact, processes can be controlled. They can be understood and controlled. And this is a very good reason why we need to do this.

So what really has to happen? Well, I think pharmaceutical companies have to change. They have to understand and control the raw materials and that's the API and the excipients. Just think about it. The APIs we really do try to understand. Excipients are the byproducts of materials that are used in the oil drilling industry. We don't have nearly the amount of control that we have over the API.

We need to develop and understand the fundamentals of each unit operation in the process, and then we have to track key critical parameters, including in-process controls. Now, I like the PAT because it means that now we should be thinking about what things we can measure on-line so that we have instantaneous feedback on what the process is doing. And we do that during development. And then we use these parameters to characterize the process entirely. We use a subset of those to do our scale-up, our technology transfer into

marketing and the validation of the process on the commercial scale.

And then we define a smaller subset as regulatory specifications. These are the ones that we're going to file and the FDA will have the right to examine.

But we also define a larger subset of these parameters that we can use for trend analysis so that we can monitor the drifts in the process before they're disastrous.

This all makes really good business sense since it reduces batch failures and it simplifies the changes and the inspections that we're bound to have.

So staying with the pharmaceutical companies then in a regulatory submission, whether it be an NDA, an sNDA, or an ANDA, we would include a well-constructed formulation and process development report. And I know we put in reports that this has really got to be well-constructed with all the information.

Just imagine if you are an FDA reviewer sitting in Washington. You may have a background in analytical chemistry or you may have been involved in drug delivery and your Ph.D. in pharmaceutical sciences, but you have no experience of processes. And all you get is what the company sends you as the NDA without any background on the processes that the company has developed over six years.

How is that person going to really understand what's happening in that process? So they're going to be very afraid to make a change or make a decision unless they have a box to check, and that's the last thing we really want is a box to check.

So we would like to be able to have a process development report that shows the rationale for the choice of the materials and the processes and the critical parameters to control that process.

Then the company would use this document as the basis of the regulatory specifications and for review at the FDA central office. And I like the idea of the central office and the field inspectors being tied together. They understand this process, both of them, so that the validation and the change control protocols that are reviewed at the PAI would also come from the same document.

And it would also be the document that would be used in the negotiations of the regulatory pathway for subsequent changes either in composition, because we would have covered that in the process, or in the site. We went through site stability a few years ago and there was some people at the FDA that said if you change the ZIP code, you've changed the process. You had to do stability again when, in fact, what really happened was that the processes were poorly controlled, poorly defined, and when they went

to a different environment and the humidity was different or the equipment was different, it didn't work. So understanding your process and being able to do this would get around that whole problem.

Well, what has to happen at the regulatory agencies? We have to move beyond stability as an indicator of process reliability, site transfer, composition and process changes. Of course, stability is important but it's only one of a series of parameters that are important.

We have to apply chemical and material science and engineering principles to evaluation of new products and to post-approval changes.

We have to treat trend parameters differently from regulatory specifications. So if the inspector goes in and sees these are drifting, it doesn't mean that the process has failed. It means it's slightly drifting, but it's still well within control and you're going to be able to get it back in control.

And somehow the FDA has to provide incentives to encourage companies who develop and run robust manufacturing processes, either by reduction in prior approval requirements or faster or less frequent GMP inspections and lots of other things I'm sure that people could think about, so that there's a reward for people who do this well.

And that's the end of my presentation. I thank you for listening to me.

DR. BOEHLERT: We have time for a few questions for Colin.

DR. HUSSAIN: Colin, thanks for that presentation.

This was a discussion I think that occurred in early parts of the PQRI. I don't think we had formed the PQRI yet. So it was Larry Augsburger, myself, and Colin sort of discussing this, but it never went anywhere in PQRI because I think it was too much out-of-a-box thinking at that time and probably still is.

But I think "make your own SUPAC" or "create your own SUPAC" makes logical sense in the way I think we have to do business. I think the comparability protocol just is a reflection of this but not to the extent I think I'd like to see that happen because I think if you really have process understanding and knowledge and you can predict, then I think you can have so many rewards coming from that. That's the reason I wanted you to listen to this presentation.

DR. BOEHLERT: Tom?

DR. LAYLOFF: I agree with Ajaz. I think defining the robustness around the various control points is really critical. Essentially you build your own SUPAC

because you define the robustness around each control point. That's what should be what's in development and it should be there. I think building your own SUPAC is the only way to go.

DR. BOEHLERT: Gary.

DR. HOLLENBECK: Colin, that was really good.

The question I would ask you is, if I recall things right, I think this philosophy was espoused in SUPAC. Certainly there was language in there that encouraged people to establish validated ranges and there were rewards for doing that and for working within your validated ranges. And to the extent that my memory is correct there, I guess that wasn't enough, was it? That wasn't incentive enough for the industry to really pick up on that. Is that correct?

DR. GARDNER: I think that's probably true.

DR. HUSSAIN: And I'll add SUPAC '95 allowed only one change. And how do you manage a change in a multifactorial system when you're just allowed to do one change? What did that mean?

DR. BOEHLERT: Other questions or comments?

(No response.)

DR. BOEHLERT: If not, I'd like to thank the speakers and the committee members for this morning's discussion. It was a very good discussion.

We will reconvene promptly at 1:30.

(Whereupon, at 12:10 p.m., the subcommittee was recessed, to reconvene at 1:30 p.m., this same day.)

AFTERNOON SESSION

(1:30 p.m.)

DR. BOEHLERT: I'd like to welcome you all back to the afternoon session. We have two presenters right after lunch. First is Kenneth Lavin.

MR. LAVIN: Good afternoon. On behalf of the GPhA, I'd like to thank you for allowing me to speak with you regarding this initiative. We believe that this program is an important step in clarifying the pharmaceutical industry's requirements for providing safe, effective, as well as affordable pharmaceutical products to the American public.

At the recent workshop, we heard several broad ideas and concepts put forward to improve the quality systems within industry, as well as within the FDA. While GPhA supports any program that will improve our ability to deliver high quality pharmaceutical products, we believe that much work needs to be done in the area of providing guidance and training on the various programs and ideas expressed at this workshop.

While it's intuitive that implementing a risk-based approach to quality systems is appropriate, what was apparent was the lack of understanding as to what this will entail when the day is done. That is, even the definition as to what is risk and how to mitigate risk and the

codification of such a program could not be agreed upon. What we have not heard is exactly how this will be implemented and what the ramification of this approach will entail especially when it comes to enforcement. The GPhA is requesting that as the details of this program get fleshed out, the FDA, in conjunction with the different industry coalitions, continue a dialogue on this topic to ultimately develop the appropriate guidance and education forums prior to its implementation.

In addition to further defining the risk-based approach to current good manufacturing practices, we believe that certain of the topics or ideas presented at the forum need further definition and appropriate guidance put into place. Among these are changes to approved applications, the CMC review, and the inspections.

One of the items of discussion revolved around changes to approved applications and approval of applications with interim specifications. Along with the adoption of this approach would be the necessity for firms to file some kind of development report. GPhA would support such a measure if there were some definite guidelines published on what is necessary to be included with these reports, how the information in the reports would be used, an assurance that there would be no negative impact on the review of these reports, and an expectation

that the filing of these reports would improve the approval times of later supplements. Again, we would urge the agency to prepare guidance documents on this topic, outlining the requirement of the program with a clear understanding of the goals that are to be achieved.

With the current resource constraints placed on the FDA, we believe that a review of the preapproval inspection program be performed. Utilizing some of the principles of a risk-based approach, we do not believe that the preapproval inspections are necessary for most of the applications that are being filed. We do agree that some inspections may be necessary for novel compounds or formulations or for products utilizing new technologies. Further, while the presence of chemistry reviewers on the inspection teams may be beneficial in the long term by providing an excellent training forum, we question whether their time spent out of the office will cause delays in the approvals in the short term.

A large portion of the discussion centered on communication issues. A 483 dispute resolution system consistent across all districts should be implemented. We believe that additional information sharing issues should also be addressed. Internal policies of the FDA should be made public. Written requests for information, for example, control documents, are not responded to in a

timely manner. Further, information contained in these requests, once deemed releasable, should be made available to the public as soon as the determination is made. Publishing this information on the Internet would be a viable approach.

A process for requesting and holding pre-ANDA meetings should be proceduralized and not be perceived as an unusual request. We believe that the best approach to timely approval of applications and providing the FDA with all of the information they deem necessary would be enhanced by more open and forthright communication.

By providing the industry with these guidance documents and procedures, we believe that the goal of protecting the American public and providing safe, pure, and effective products is assured. Industry cooperation and input into these guidance documents is paramount to the success of this program. Inspection and review based on these documents will provide consistent compliance and provide our industry with the needed information to consistently supply pharmaceutical products in an economical and timely fashion.

Finally, the GPhA looks forward to continued dialogue on the subject and supports the FDA in this endeavor. We stand ready to provide the needed input into this program and are willing to serve on any committee or

task force empaneled.

DR. BOEHLERT: Questions for Ken? Tom?

DR. LAYLOFF: Yes, I have a couple of questions. One of them is on the definition. Helen this morning put up a definition of risk management was to ensure that systematic risk management approaches are applied to allocating resources, selecting sites for inspection, and determining the scope of GMP programs for human and veterinary drugs, which is an FDA vision for their risk management. Do you think that's unclear?

MR. LAVIN: Well, it's unclear when it comes to enforcement. Does a particular investigator's observation warrant continued review of a firm? How serious an observation does it have to be in order to --

DR. LAYLOFF: That's a 483 dispute resolution issue.

MR. LAVIN: Yes, but we're talking about the enforcement side of it.

DR. LAYLOFF: This was on the risk management from the FDA perspective.

MR. LAVIN: I think the details of this program really need to be fleshed out a little bit better than it has been to date. We're just cautioning the FDA to take their time to develop the program before proceeding.

DR. LAYLOFF: Another question I had was you

noted that they should publish the control docs. Does that mean when a control doc is made public to one, it should be made public to all at the same time?

MR. LAVIN: That's correct.

DR. LAYLOFF: So as soon as it's released to one, it should be public on the web site for all.

MR. LAVIN: That's correct.

DR. LAYLOFF: Thank you.

DR. BOEHLERT: Dan?

DR. GOLD: Mr. Lavin, I'm a bit confused. On your slide on preapproval inspection, it says, no longer universally necessary. I thought preapproval inspections from the outset were not mandatory if the firm were following essentially the same type of technology and it was within the two-year time frame. Is that not the case any longer?

MR. LAVIN: From my experience, at least in my district, they were managed pretty well. What I am hearing is there are certain firms that are routinely getting preapproval inspections for similar products, similar profiles, and the like. It's not a consistent approach.

DR. GOLD: So it's the consistency of --

MR. LAVIN: Well, that's what we're asking for. Obviously, if there are new products or novel technologies, then it would trigger an inspection, but to

repeatedly have an inspection, regardless of the class of products that you may have been cleared on before, really needs to be evaluated.

DR. GOLD: Have those firms approached the agency and asked why the policy that's been stated, that's in writing, is not being followed?

MR. LAVIN: I'm not aware of that.

DR. GOLD: But the word "universally" then in your slide is perhaps misleading because you said your firm has not been subject to repeated inspections on PAIs.

MR. LAVIN: Recently. But we've had preapproval inspections. Part of the preapproval inspection program was with the top 200 drugs. If one of your products fell in that, that triggered a preapproval inspection regardless if it was a simple single ingredient solid dosage form. If it was on that list, you'd get it again. So there's really a haphazard -- no, not haphazard -- maybe not a well-defined system because if you choose the top 200 products simply to trigger a preapproval inspection, there's no assessment of that.

DR. GOLD: Joe, do you have any comment on this reported inconsistency of this program?

MR. FAMULARE: I was hoping you meant Joe Phillips.

(Laughter.)

DR. GOLD: No, no. He's no longer the official spokesperson.

MR. FAMULARE: We have, in our compliance program, set criteria for conducting preapproval inspections and some of those are set in terms of, as you said, the top 200, new chemical entities, et cetera. Once we go through that list, then it's pretty much at the option of the preapproval manager, or it may never even reach the preapproval manager.

One of the first steps that we've taken, in terms of cutting down the frequency of preapproval inspections, you might call a back door approach, but it was enhancing our GMP inspection program through the systems-based inspection approach. Many GMP inspections that are conducted are for the reason that we're not able to keep up on a two-year basis on the GMP compliance status and we keep doing these short preapproval inspections because we haven't been there, and we don't do systematic coverage of the firm.

Under the new compliance program that issued February of 2001, if we cover the minimum number of systems, we will mark all the profile classes so that individual inspections against a particular profile class should no longer come up. So we see the need to even further tailor preapproval inspections, but they're not

universally done. They're selected, and probably for every one you see done, there are many, many, many that we just make the decision on a daily basis not to do based on other information we have.

DR. GOLD: Thank you.

MR. PHILLIPS: Could I comment on that?

Just to support what Joe is saying, I myself come from a long career with FDA and was rather closely involved with the PAI program. I've been out of the agency for two years. But exactly what Joe is saying was the case then and I suspect it is now.

Preapprovals were not mandatory 100 percent of the time. In many of the districts, the preapproval managers opted not to do a preapproval if there was sufficient case history there of a firm consistently meeting its commitments and complying with GMPs. So I think that is the situation. I used to see many of the decisions for making PAIs and those for not making them, and they were rather consistent across the country.

DR. BOEHLERT: G.K.?

DR. RAJU: I just wanted to make sure I've compartmentalized. It's clear that the FDA can improve on a lot of fronts, particularly on the investigation front, and that's the history, if you go back many years, on the many things they can improve.

But in terms of your feedback and your opinion, I wanted to see if we could separate that from the actual GMP initiative itself. Do you believe that in terms of being clear and in terms of positioning the future, they have not been? Because if you look at the PAT Subcommittee or the PAT effort before and what I've heard in six months from the FDA, in my opinion they have been the faster ever in terms of the PAT Subcommittee, in terms of being clear about the principles. I was very skeptical in the beginning, but I thought they were surprisingly fast and surprisingly open-minded. So is your view more about the practices of the past or is it about the cGMP initiative itself?

MR. LAVIN: Well, just to step back a little bit with the PAT initiative, while I think the endpoint is something that is pretty well defined -- I mean, having the desire to have firms implement this to enhance their quality systems, I think that goal is pretty well fleshed out. But we're still having these little sub-arguments about, okay, once you start capturing this information using the PAT, what are you going to do with it? So while, yes, maybe in PAT the goal is defined, the incremental steps of the program and what to do with that information has not been fleshed out.

What the worst thing in the world would be, I

think, for a firm would be to implement some PAT technology and then find themselves holding a bag of information that they can't do anything with. Now, we've heard talk about the safe harbor portion of the program and the like, but those things really need to be put down on paper. Much like we have inconsistencies from district to district relative to a 483 item, in one district a PAT -- dealing with the information may go pretty well. In another one you might as well shut your product down and move somewhere else.

We're really stressing the need for guidance in these things. Tell us what you want. Tell us how to deal with these things, who to talk to, how to resolve these issues. Once we get down and have the rules on paper, I think the game will be played a little more easily.

DR. GOLD: I have one additional question, Mr. Lavin. How in your opinion are the procedures for the pre-ANDA meeting -- and you talk about proceduralize the pre-ANDA meeting. How are they different currently from the pre-ANDA meetings that occur?

MR. LAVIN: Well, currently there is no procedure for having a pre-ANDA meeting.

DR. GOLD: So you mean at times you're not called in for a pre-ANDA meeting?

MR. LAVIN: Oh, I would say -- 100 percent is a

pretty high number, but 99.99 percent of the time there is no pre-ANDA meeting. It's you file the application and you deal with the reviewer comments.

There are situations where one would be helpful where a firm has some questions about some technology or some of the requirements of the FDA. We'll file an application knowing there will be questions. If we could sit down or ask for a meeting and get one to talk with especially OGD, that would be helpful. And currently there is no procedure for doing that. You can ask for a meeting but it won't necessarily be granted.

DR. GOLD: How do you see that a pre-ANDA meeting would help the generic industry?

MR. LAVIN: Well, as I said, there are applications that will go in where we know there will be a question either from a bio reviewer or a CMC reviewer would have. If we could sit down and talk about it, how it should be filed, how it should be highlighted in the file, how it should be presented to address this problem instead of waiting for the first review letter which inevitably will be a major deficiency.

DR. GOLD: There's no one here from the agency who could speak for the generic division, is there?

MS. WINKLE: I can but we're in the process of looking at the various processes in OGD and in the process

of starting to meet with industry, not an individual basis but a broader basis, to talk about some of the areas in the process where we could make improvements, and that's certainly something that we could consider. I don't know that we could do it in every case, but there are certainly cases where I think there are significant questions that could be answered and save both sides problems. So I appreciate it.

MR. LAVIN: Right. If there were just a procedure for allowing them to happen instead of "you want to come down and do what" type of reaction would be beneficial for both sides.

DR. BOEHLERT: Ajaz?

DR. HUSSAIN: I just want to share my perspective. From a PAT perspective, I think Ken mentioned that we still have a discussion, what do we do with data and so forth. I think from my perspective that's an issue that I think companies will have to grapple with. If you have volumes of data and you don't know what to do with it, then I would say you haven't understood the process that you're trying to do. So I don't think we can help in that regard.

MR. LAVIN: Well, that's not necessarily true. You're testing every single tablet maybe for content uniformity, whereas the current test is you test 10 tablets

and the spec is 85 to 115. You're testing every tablet now. What is the acceptance criteria? You're going to get a tablet maybe that's 84 percent. How is the investigator in the field going to come out and say, here's evidence right here that your product is not uniform. So from an enforcement standpoint, while a firm may be well justified with the way they handled that particular data point, there's still that second guessing coming on.

So without guidance on this, a firm is putting themselves at risk. They're going to have to have data that they're going to have to answer to.

DR. HUSSAIN: I think the way we approach the guidance it will have that, but the guidance is not going to solve any problems in terms of giving you a cookbook. It's not going to be a cookbook guidance.

MR. LAVIN: No, no, no.

DR. HUSSAIN: It's going to be a guidance which simply defines the general principles of saying we'll use sound statistical principles to evaluate that. You have a new method. You have to have acceptance criteria that is consistent with the method. That's about it.

MR. LAVIN: It's still open to interpretation.

MR. FAMULARE: The GMPs require that it be scientifically sound and statistically valid. So to use a measuring stick -- and we were talking about measuring

sticks this morning -- against what you do for 10 tablets versus the whole batch would not be valid.

MR. LAVIN: I agree with you. I agree with you entirely. Now, you're going to have every investigator in every district thinking the same way or you're simply going to get that opinion document --

MR. FAMULARE: The other approach we've taken in terms of the PAT realm, realizing these nuances, as has been mentioned many times by Ajaz, is the dedicated team, a small group of people to start this process. So that was one of the first issues addressed head on. Not only the investigators, the reviewers, they're all in that same boat.

MR. LAVIN: We certainly understand that. What we're asking for is have the details fleshed out in a guidance before we launch into this.

MR. FAMULARE: But again, to the point Ajaz made, a guidance can take us so far and then we have to apply science and reason to get to the answer. That's the process that we're working on.

MR. LAVIN: I agree.

DR. LAYLOFF: I was going to say you could write up your own criteria. I mean, you could say if you analyze 10 tablets, you fall in this range. If you analyze 100 percent of them, you go with a standard deviation of 6

percent, and that's it. You meet the USP criteria in the broadest sense, but not in the very narrow definition.

DR. BOEHLERT: Joe?

MR. PHILLIPS: Sure. I just want to give my perspective from the 10,000-foot level of the overall initiative. Just back up a little bit. I've been out of the agency two years. I've worked with the industry. I'm not with an association.

But I think this is a very, very bold step for the agency to take. They took a system, which in my opinion wasn't broken but certainly can be improved. They looked at themselves internally. They listened to the industry, to academia, to associations, and they identified a number of initiatives, all of which in my opinion are very substantive.

There's a lot of work to be done on all of those initiatives by FDA. There's a lot of work to be done on all of those initiatives by academia, by industry, consultants, associations. So now is the time for us outside of FDA to step up to the plate and give them support on this new initiative.

When I first saw the initiative in August, I asked myself is this rhetoric or is this going to happen. The February progress report came up and there was a lot of progress made. If nothing else happens than the Part 11

changes, it's substantive to the industry.

So I just commend the agency and I encourage you to keep going forth. I heard you ask for any other initiatives. If we have them, we should be coming up with them for the agency.

DR. BOEHLERT: Any other comments?

(No response.)

DR. BOEHLERT: Ken, thank you.

MR. LAVIN: Thank you.

DR. BOEHLERT: Our next speaker is Gerry Migliaccio.

MR. MIGLIACCIO: Good afternoon. I am Gerry Migliaccio. I am the Vice President of Global Quality Operations for Pfizer, and I am here representing a PhRMA perspective.

The way I'd like to do that -- you've heard a lot about the FDA PQRI workshop that occurred a couple of weeks ago, and what I'm going to try to do for you is in 15 minutes distill down two-and-a-half days of very exciting discussion. What I hope to represent is what the industry input was to FDA at this workshop. Joe, you stole my first slide in what you just said. So thank you.

(Laughter.)

MR. MIGLIACCIO: The PhRMA perspective on the quality initiative is that there has been significant

progress to date. We have been advocating science-based guidance and regulation. We've been advocating a lot of things. When your first announcement came out, we had the same impression that Joe did. It was sweeping. It was ambitious, but when we saw the status reports, we were very impressed.

More importantly, we were impressed at the organization and the commitment to the workshop in April. There were 500 people at this workshop. I think there were well over 100 FDA representatives, the rest industry and consultants, but there was a significant commitment to the process.

The industry is very supportive of this initiative and we are trying to contribute in any way we can. We think it is a once-in-a-lifetime chance for all of us to move the state of the regulatory processes around, pharmaceutical manufacturing up to the state of available technology. We're in violent agreement on many issues, conceptual agreement on others, and somewhat disagreement on very few issues, and I think those will resolve themselves.

We definitely considered the workshop a success. I personally thought that the views were expressed openly and we got a lot of good value out of those three days.

So let's talk about what that workshop was about. There were four individual workshops. The first was risk-based GMPs; the second, integrated quality systems approach; the third, changes without prior approval; and the fourth, manufacturing science. A day at the beginning with academia, FDA, and industry giving introductory talks on these four subjects, a day of intensive workshops, and then a half-day of summarizing the workshops.

Significant overlap in the discussions and the findings from all four workshops. That was not unexpected. In the planning of the workshop moderators, it became very clear that there was going to be overlap, and that's the good thing. There is no way you can divorce the whole concept of risk and risk-based from any of the other subjects. Quite honestly, as G.K. has said, there's no way you can divorce the concept of science from all of them. Therefore, there was significant overlap and a lot of commonality in the discussions.

But now it's time to operationalize those concepts. I'm the first manufacturing quality person here, practicing one. So we want to operationalize, and it's time to move on to that.

G.K. uses pyramids. I'm a practicing quality guy. I can't use pyramids. I have to use curves, things like that, because pyramids imply that you get to the top

of the mountain and you're king. That's not a politically correct thing to do in industry.

What I'm going to try to do is paint this manufacturing science and risk model which really came out of this three-day workshop. Let's first look at manufacturing science. It's a continuum. There are three key elements to manufacturing science. Product and process knowledge is the first. What do you know about your process? Technology is the second. What manufacturing technology are you using and what process control technology are you using? And finally, the third is the underlying quality systems infrastructure. How good are the quality systems at the manufacturing site?

As you go up the manufacturing science curve contributing from all three of those elements, you gain a higher knowledge and better control over your processes. More importantly, you have a greater ability to predict what will happen when you make a change to those processes. And that's what's key here. If I have a change or a deviation, an event, can I predict what will happen? Will it impact the fitness for use of the product?

So we are struggling with what do we mean by fitness for use. Well, we mean at the base level safety, efficacy. Others will add convenience to use and availability. So let's use that as a definition now.

Will a change impact fitness for use? The higher you are on the manufacturing science curve, the greater the ability to predict that.

So then you overlay the risk curve. The risk of a change, an event, a deviation impacting fitness for use goes down as you go up the manufacturing science curve. But it is important to note that it does plateau. Technology for technology's sake is not always the answer. There is not a gain. For certain products and processes, for certain unit operations, there is no further gain in risk reduction by investing in more technology. That's just an important point to realize.

Now, in the end what we're looking at is trying to take this manufacturing science and risk model and overlay a flexible or tiered regulatory process. I'm not proposing that there are only three. I will go with G.K. and say maybe there are five. But a tiered regulatory process model which goes along with this, which provides the flexibility for a firm who has demonstrated that they know what the impact of a change or a deviation will be on their product, to innovate in a more timely manner, to demonstrate to themselves scientifically that they know what the impact of the change is, that they know that there is no impact on fitness for use, and to make that change, to innovate in a much more timely manner without

significant regulatory hurdles is really what it all distills down to from the three days of workshop. A PhRMA group sat around a room and drew this out in about three hours. This is really what it means to us.

So what are the prerequisites for this model? The first is culture change. And I'll go through each of these individually. The second is knowledge sharing, and you heard this from David this morning. We can't be in more violent agreement that we have to share knowledge, but it's the right knowledge -- not more knowledge, the right knowledge. Risk management principles. You've heard this from everyone, and finally the whole concept of an integrated quality system. These are the prerequisites to achieving the ultimate goal of a good manufacturing science and risk model.

Let's talk about culture change. Every workshop, all four, the first thing on the slide, trust, both ways, not just industry being able to trust FDA, but FDA being able to trust industry. The trust to be able to share knowledge and have that knowledge used in an appropriate fashion.

Open communications. More than once we heard in a workshop somebody from industry say, well, we can't approach the FDA. We can't get a hearing on this, and to have the FDAers say, well, our doors are open. The

communication just wasn't there on how to get that into the right communication link.

Helen mentioned this this morning. We have to move from "change is bad" to "change is good." Change is bad. You've heard a couple of people talk about this. When you develop a product and you put it on the market, one of the worst things you can do is then try to change it because the regulatory hurdles just keep spiraling upward.

Most of us will readily undertake a process change for an API because those process changes for APIs have real gain in safety, environmental control issues. They're beneficial, and we try to continually improve those processes.

On the drug product side, there are very few that have those safety and environmental impacts, and you have to make the decision whether you're willing to go through the regulatory hurdle to make a change that would improve the process. So that is a difficult decision.

We really want to move to "change is good." We want everybody to say that change means innovation and change is good.

I've said it before, but fitness for use by the patient has to be the key driver for both FDA and for industry. I acknowledge that we still have to work on what we mean by fitness for use, but I think fundamentally we're

talking about safety and efficacy to the patient and availability.

Knowledge sharing. A lot of discussion at the workshop about knowledge sharing, and probably the fundamental concept that we really need to get our arms around here. What does FDA need to be able to ascertain the level of understanding that we have about our formulation, our process, and the potential impact of changes on fitness for use? So in the end what that means is what does FDA need to assess risk. That's what we're really getting at. What is it that they need?

We have a large database. We share a portion of that with the FDA. Currently we're probably not sharing the right portion of that. We have to decide what is the right portion. Again, I have to stress it's not more. It's the right knowledge.

The key concern of industry is how is that information going to be handled? Is it going to delay the review and approval process of an NDA because we are sharing a different knowledge base? Or is it going to be used in a very scientific sense to help support and facilitate the review and approval of the NDA?

What kind of knowledge are we talking about? Development pharmaceutics clearly. Critical-to-quality attributes and parameters. Have we identified them? Do we

know what they are? And more importantly, do we know what the impact of variation of those are on fitness for use? And as G.K. mentioned, process capability. If we can provide at an original NDA or in a supplement to an NDA after we have more commercial experience this kind of knowledge, we believe this should allow the agency to look at this product or process and say it is low risk, it is moderate risk, and therefore the regulatory processes associated with it will be less burdensome.

Risk management principles, the area that needs, as we've already said, the most development, but risk assessment. What's the process going to be? When I talk about risk, I'm talking a very narrow scope of risk. I'm saying what is the risk that a change to my manufacturing process or a deviation that occurs during manufacturing will have an impact on fitness for use. That's a very narrow scope. We've talked about risks associated with inspections and what level of inspection should a firm have. That's a different level of risk. But we need a risk assessment process.

And we need to agree on risk mitigation strategies. You saw the manufacturing science curve and the associated risk curve. Now, I may have a very complex product which you would put at a high risk initially, but if I use certain technologies, certainly process analytical

technologies, to monitor, provide continuous feedback, I should come down the risk curve. I should come down that risk curve. And that is certainly what we are striving for, and I think that's one of the things that the agency and the industry are in violent agreement on. It's just a matter of how do we demonstrate to each other where we are on that risk curve.

And then risk classification. How do you classify a -- and I don't think it's a firm. I don't think you can classify a firm. You might be able to classify the underlying quality infrastructure at a firm, but it's a product or a process and it's a manufacturing site, but I don't think you can classify a firm unless a firm is one site with one product. Because people ask me where is Pfizer on that manufacturing science curve, and I will tell you we're every place on that curve, depending on the product. Depending on the product, we are everywhere on that curve, and I think any other company would say the same thing.

So the definition of risk is still a work in process, as you heard from David, but we have to remember that risk does change through the product life cycle. The more knowledge you have, as you gain experience in commercial manufacturing, the more technology you apply to that manufacturing process, you can mitigate risk, you can

change the risk factor. So because at the time of NDA approval we assign a certain risk to a product, it doesn't mean that that carries that risk for the rest of its life. It will change.

The integrated quality system. Now, here's where I lumped in a lot of very good input from the workshop, and I think it really does come into the whole concept of an integrated quality system within the agency starting with science- and risk-based GMP guidance documents. I think PAT is the model. Aseptic is right on the doorstep as well. I think these are becoming now the model of how to do it and how to get it out.

Knowledge transfer between the center and field is critical. I think the pharmaceutical inspectorate will facilitate that. If we're going to share knowledge with the center, it also has to get out to the field or we haven't accomplished much because you'll have the inconsistencies that were talked about in the last presentation.

This whole concept of specification life cycle. You heard interim specifications in the last presentation. I've gone away from that concept just to a concept of specification life cycle because if you are monitoring process capability, then as you go along and you learn more and more about your process capability, you really should

reevaluate your specifications, and that's really what we're about with the specification life cycle which really was born out of the original idea of an interim specification.

And then flexible regulatory change management process. First of all, it starts with the original knowledge base that we transfer to the FDA, and it should lead to more changes that do not require prior approval. What we're saying here is that we have demonstrated to ourselves and to the agency that we understand this process and we understand the impact of changes on this process. Therefore, you can use the "make your own SUPAC" terminology if you'd like, but I've put the boundaries around what change I can implement because I've already demonstrated that I understand what the impact of changes like that will be. So that's really what we're getting at there.

Now, I have a few bullets here on inspections based on risk assessment. Before I get into my slide, I would like to address some of the comments from this morning on 483s from kind of the real world of having to deal with 483s.

More than 10 years ago now, when most of your inspections were what we'll call general GMP inspections and you received a 483, you had the ability to evaluate,

decide did we actually explain this properly, should we go back to the district and discuss this further, should we appeal, whatever. That's 15 years ago when you had the luxury of time to do that because, first of all, the time it took to get from a 483 to a regulatory letter at the time was significant. So you had the time to have a discussion with the district and try to put more scientific rationale behind your argument of we're doing it this way because it makes scientific sense and we think it's a valid way to do it. So you could take that time.

With the implementation of the preapproval program, most of the inspections we get now, as David said, are preapproval, which means there's a new product waiting to be approved. And if you look at G.K.'s slide about manufacturing -- you know, make sure the product is available, don't be on the critical path, that's very valid. That's a business reality.

So I have made decisions to implement policy or practice on a global basis based on a 483 because if I don't, the product won't be approved. Why? Because right now there is no dispute resolution process. Right now there is no ability to get a timely resolution of an issue like that, and right now it takes a very short period of time to go from the 483 to the warning letter.

Now, I say all that and now I will add we are

very supportive of the dispute resolution process that is in development. We are very supportive of the fact that the center is reviewing all warning letters now because we do believe that will lead to consistency and predictability. We're so supportive of this initiative because the FDA understands what the issues are and are addressing them one by one.

So that's why the industry has reacted to 483s and will continue to react to 483s in the context of preapproval inspections where a new product approval is hanging out there and if the district says that's what they expect, then that's probably what we're going to do until there is an effective dispute resolution process to enter into, and we're hoping that's right around the corner.

So I just wanted to add that to this morning's discussion on 483s.

We do believe that inspections should be based on a risk assessment, and I think that's uniform. What is the firm's and the site's prior compliance record? The product type and the process complexity, the level of risk associated with it. The facilities and the technology used. Are we talking about aseptic? Are we talking about direct compression, solid orals? What are we talking about?

We think that there should be more of a focus

on what I consider the more value-added systems inspections. Why do I say the more value-added? They give the agency one of the elements on that manufacturing science curve. What is the underlying quality systems infrastructure at the site? That contributes to their ability to understand the risk, the level of science we're at, the risk associated with our operations. We think the focus should be on those types of inspections versus the preapproval, which has turned into more of a documentation review and doesn't say much about the underlying infrastructure unless they turn the preapproval into a systems inspection as well.

So the next steps. I can never leave one of these talks without saying what I think we ought to be doing, and so what I'm going to do is point out a few focused workshops that I think we should be having. By we, I mean FDA, academia, and industry, and I would hope that this subcommittee would be driving the impetus to get to these workshops.

The first clearly is what is the knowledge base that needs to be transferred and how will it be handled in the regulatory process. So going back to one of my first slides, what does the FDA need to assess risk and how will that information be handled to facilitate the process, not to delay the process?

As David said, we need to define what we mean by risk, what risk assessment process will we adopt, and what are the risk mitigation strategies. What do we believe will effectively mitigate risk?

We need to continue the focused workshops related to science-based GMP guidance. Process analytical technology again is on the doorstep. You're going to hear about aseptic tomorrow. OOS is another one, a draft guidance that's been sitting there, which we really would like to see come out. It's very critical during inspections, and having a finalized guidance that we all agree upon is critical.

Certainly cleaning validation is another area. This is an area where the technology now has far outstripped fitness for use. You can see down to levels that mean nothing to the fitness for use of the product, and it's critical now that we get some guidance around what is really important in the cleaning validation area.

Finally, this concept of developing a proposed guidance for specification life cycles I think is a workshop that should be held. This is very much a new product focused workshop with the continuation, the life cycle concept built into it.

Finally, the tiers that I showed earlier. What are the change management requirements for a given product

based on where you are on the risk curve? What should they be? They obviously will vary from prior approval to CBE to annual report. Some had suggested at the workshop a changes already effected supplement which would be a more timely supplement than an annual report but have the same effect of essentially it was already implemented because you had demonstrated that it would not impact fitness for use. But that certainly is another workshop that we're recommending.

So that's the end. I've tried to, like I said, put two-and-a-half days into a very brief presentation. Questions?

DR. BOEHLERT: Nozer.

DR. SINGPURWALLA: Well, I have two questions. I'll start with the first one which is a comment. Your picture on manufacturing science and risk model I claim is misleading, and I'll tell you why. If I were to look at that picture, the sense I get from it is less effort is the breakeven point between your manufacturing science curve and the risk curve. I grant you that these curves are subjectively drawn, but one could get the general impression that really to reduce risk, you really don't have to put in much effort because the tradeoff with manufacturing science would come in the way.

MR. MIGLIACCIO: Yes, and I acknowledge that.

The terms "impact" and "effort" were put there. You could have put investment.

DR. SINGPURWALLA: You could have drawn a different curve and shown that you really need to put a lot of effort to get rid of risk.

MR. MIGLIACCIO: Most of the risk is reduced with very little effort, if you look at the curve.

DR. SINGPURWALLA: That's the impression that the curve gives.

MR. MIGLIACCIO: And I believe that you can get a significant reduction in effort with a reasonably significant capital investment. Let's say if want to talk about PAT. There is some significant capital investment, but that will lead to such an increased knowledge of your process that you will bring your risk down significantly. So you can talk about effort, investment, whatever. It's at the other end of the curve that we were trying to make the point that you can continue to make a lot effort after a certain point, and it's not going to reduce your risk any more. That's really what we were trying to draw.

DR. SINGPURWALLA: Let me just reemphasize the point that these curves may be realistic, but to a skeptic like myself they may not be and you may be asked to explain.

There are two points. One of your slides says,

"definition of risk, still a work in progress." From my perspective, risk has been defined, maybe not defined in your particular context, but there is a general definition of risk and any tampering with the existing definition will essentially cause you to introduce a new definition. And where does that process stop?

MR. MIGLIACCIO: I --

DR. SINGPURWALLA: Let me make my third point and then you can answer.

The third point is on your last slide, you said inspections should be based on prior compliance record, product type, and process complexity risk. I grant you that, but there is a danger. Suppose you have an organization that has an excellent compliance record when it comes to uncomplex processes, but when it comes to complex processes, it may not have. So there could be a negative correlation between those two. We want to be sure that --

MR. MIGLIACCIO: No, no. In that you misunderstood what I said. The need for inspections should be based on risk. If a facility which has never made a product of that complexity is about to introduce a product of that complexity, regardless of prior compliance risk -- and I think the speaker before me said the same thing -- new technologies obviously are going to beg

inspections. Moving from what you've done for 20 years to a totally new paradigm in manufacturing, obviously we would expect that the FDA would be coming in. That's not the issue at all.

But let me go back to the risk. I think what we're trying to grapple with -- and maybe David will support me on this one -- is what does risk mean or risk-based mean in the context of this quality initiative. When this started, Janet Woodcock gave three separate different definitions of risk, not so much definitions of risk, but the type of risk we were talking about. And that's really what we're saying. What risk are we talking about here? I talked about a very narrow focus of risk, and that is the risk of something, a change impacting fitness for use of the product. That's what we're trying to grapple with here.

David?

MR. HOROWITZ: Yes. I think this actually might be one of those issues in which we're in violent agreement.

But I think risk is actually very easy to define, and the generic definitions that I talked about, the key elements being the severity and the probability of harm or exposure to a particular defined hazard. Those are concepts that run throughout the different disciplines that

have applied risk in various contexts.

But the real challenge is applying those more general concepts to drug quality and to drug regulatory quality oversight. And that is something of a challenge because we can define the harm that we're after in many different ways, and the way that we define that harm will ultimately determine how we quantify and thereby assess, prioritize, and manage risk.

DR. SINGPURWALLA: Can I react to that please?

DR. BOEHLERT: By all means.

DR. SINGPURWALLA: There's only one definition of risk: expected loss. How do you calculate expected loss? Two ingredients: probability multiplied by utility.

MR. HOROWITZ: Yes, but the challenge is loss of what.

DR. SINGPURWALLA: Whatever it is that you're looking at.

MR. HOROWITZ: But that's the challenge.

(Laughter.)

MR. MIGLIACCIO: That's what we're trying to get around.

DR. SINGPURWALLA: But that is different from defining risk. What we are discussing here is how to apply well-known, existing technologies to a particular application. I took a taxi this morning to come here, and

I wish I had taken the Metro because the taxi driver was driving rather aggressively. I made a decision. It was a risky decision, and it's a question of an application.

I think what this committee should be looking at more carefully is not how to define risk but more so how to apply the existing definitions and the existing notions. The most difficult job in doing risk analysis is calculating the correct probabilities. That takes a lot of effort. Calculating utilities. That takes a lot of effort. The principles are all well established, and this group, including myself, is not going to change those principles because they have been around for 250 years. That's the only point I'm trying to make.

DR. BOEHLERT: Other comments, questions? Yes, Ajaz.

DR. HUSSAIN: I think the fundamental issue is fitness for use, the definition of that. I'll sort of share my perspective on that. The way we have practiced, specifications are fitness for use. The scientific process of establishing controls and specification is intended to define that use of a product which essentially defines its intended use. So from that definition, quality essentially is at one level ability to meet your specifications, and those specifications have to be meaningful and science-based and so forth.

In modern terms, quality is also defined as customer satisfaction. In that regard, I think in pharmaceuticals that has always been a challenge. In a clinical setting, you really don't have the tools necessary to define whether the product really worked or not.

So it really boils down to your specifications, quality. Therefore, risk is not able to meet those specifications. So that's the current model. So how do we move from that model to something better would be one of the topics for discussion.

DR. BOEHLERT: One last comment and then we'll move on to the next presentation.

DR. HOLLENBECK: I'll save it.

DR. BOEHLERT: Okay. We're going to have plenty of time for discussion.

I think Ajaz is on next, and he's going to tell us what this is all about. Right?

DR. HUSSAIN: My goal here is to actually share some thoughts with you to essentially have you discuss and identify topics and their prioritization for several meetings that you will engage with us.

Both Helen and David have outlined the goals and objectives and the activities under this initiative. One of the tasks that we were asked to do was to essentially define the vision for the future because all

these goals and objectives are fine, but we do need to know where we are going so all these activities lead in a meaningful way to this desired state or vision. So I'd like to share with you the desired state or the vision for the future, and we believe this has become a shared vision for the future. And I'll pose that question to you, if you agree or not.

Next, I think we would like to identify and prioritize topics for discussion. As Gerry said, we want to move towards creating a system that really starts working now. We'd like to hear your recommendations on a format and background information FDA should prepare for discussion of identified topics. So this is the task for you this afternoon, the discussion this afternoon.

We have kept sufficient time for this discussion, and based on what I have seen this morning, the time may not be sufficient.

(Laughter.)

DR. HUSSAIN: But you may surprise me.

So this is what will happen this afternoon.

Tomorrow what we would like to do is update you on current activities, the PAT initiative and how that fits into the drug quality system for the 21st century initiative. We'll share with you comparability protocol as a tool for continuous improvement. I think this goes hand

in hand with what Colin presented this morning. I would like your discussion on the comparability protocol and what opportunities still remain to be realized. Is this approach on target or should we be thinking more in line with what Colin Gardner suggested this morning? And you'll hear Dennis Bensley, who will summarize this comparability protocol for you, tomorrow.

We also wanted to share with you a perspective on risk analysis. Our risk expert will not be here tomorrow, but we hope to get his comments in today. He has already seen the presentation. This is a presentation from a CVM person which was presented at the workshop also, essentially bringing in concepts such as failure mode/effect analysis and so forth and just get the thought process on risk system models and so forth started because I think that one of the first topics for discussion in the discussion with this committee is likely to be the definition of quality, risk, and getting a handle on these definitions and sort of defining the concept. So at one of the next meetings, we'll focus on that.

So committee discussions on the relationship between process understanding, change management, and risk to quality would be the discussion tomorrow after you get a chance to hear these presentations and approaches.

In your program, the discussion is occurring on

the program after the aseptic manufacturing update presentation. We'd like to move that discussion up front so that we can focus our discussion immediately following these presentations. So we just want to change or tweak tomorrow's program in such a way that we end the meeting with the aseptic update because this committee has not discussed aseptic before. We had discussed that at the main advisory committee. So it's simply an update so you are aware of what's happening.

So that's the rest of the program for today and tomorrow.

Listening to the presentations this morning and what we have announced on the web site, there are five key elements that form the goals and objectives of the entire initiative. You will notice that I'm not calling this a GMP initiative. It is no longer a GMP initiative. It is a drug quality system for the 21st century initiative because it covers review, inspection, compliance, all aspects of the quality system. And it has to. Just imagine now when you set your specifications, when you approve that, and then when you're not able to meet those specifications, the question always can come back to were the specifications set right. So you cannot have a quality system that does not include CMC review, compliance, and inspection all together. So that's the reason we are calling it a drug

quality system for the 21st century initiative.

Just to sort of reiterate and summarize, the objectives are: to bring risk management; quality systems thinking; recognize and encourage scientific advancement and innovation; bring the continuous improvement process in; review and inspection programs are coordinated, synergistic, and consistent; effective and efficient utilization of FDA and I added industry resources. So those are the broad goals and objectives of this initiative.

But we can do that by changing or modifying current systems, but if you just do that on that basis and not think about the future, then I think we might miss something. So therefore, what I would like to do is to begin with the end in mind, and the end is not two years from now. The end is maybe 2020, at least the end of my career. No.

(Laughter.)

DR. HUSSAIN: So how do we begin here? I would like to start with the desired state for pharmaceutical manufacturing and associated regulatory processes in the 21st century. We announced this as part of the progress report that was issued in February. In fact, our Commissioner had ask us to define a vision for the future, and this was part of that exercise.

So as we move forward with this initiative, it is essential to define what we wish to achieve. So what should the desired state of pharmaceutical manufacturing and associated regulatory policies be in the 21st century? We think this is important because we need to have a shared vision to guide future evolution of this initiative. I'm a bit scared right now in the sense that we are in violent agreement with industry on some aspects, as Gerry put it. That's good. I think that's wonderful.

We would like to enroll all stakeholders in this journey to better serve the patients. Keep in mind we are here to serve the patients, and that's the whole objective. The patient is paramount.

But also, always linking back to the academic community where I came from, I think there is a strong need to highlight for the academic and research community the scientific needs in pharmaceutical engineering. The pharmaceutical profession, pharmaceutical engineering, industrial pharmacy are very small disciplines when you compare it to, say, the American Chemical Society or American Institute of Chemical Engineers. This is a very small fraction of those big organizations, and unless the agency or the regulatory authorities recognize the science, science will not grow in this discipline. So that has always been my concern. So I do want to highlight the need

for academic and research community and what they should be focused on.

But David actually has summarized this. I'll repeat this. Whatever approach we use, it must strengthen the public health protection achieved by FDA's regulation of drug product manufacturing. The approach should not interfere with strong enforcement of existing regulatory requirements, be risk-based and be science-based. I did not change the sequence after G.K.'s presentation. The reason for the sequence of science coming last is because I want to build on that further.

Gerry in his talk talked about trust. Now, trust is a difficult concept in a regulated industry, but I think there's a win-win here, and the win-win comes from science. The open hands is a symbol for trust. It is.

(Laughter.)

DR. HUSSAIN: I have chosen those very carefully.

Science provides a win-win approach, and the reason for this was, when I joined the agency about eight years ago, I saw such a big gap between the science out there and science practiced within the agency. I knew just filling that gap was a win-win because I knew many companies had good scientific basis for doing their development and so forth, but never shared it with the

agency. There was a trust issue. There was an issue of many different reasons.

So the win comes from just recognizing that pharmaceutical manufacturing is evolving from an art form to one that is now science- and engineering-based. It doesn't mean that we have solved all the problems. There's much more science to be done, but even just recognizing 30 years of science brings us a win.

Effectively using this knowledge in regulatory decisions in establishing specifications and evaluating manufacturing processes can substantially improve the efficiency of both manufacturing and regulatory processes. So we're looking at a win-win on both sides, and the focus is knowledge. This goes back to Gerry's presentation. What is the knowledge? What is the right knowledge? Not volumes of data, not volumes of submissions.

The initiative is designed to do just that through an integrated systems approach to product quality regulation founded on sound science and engineering principles for assessing and mitigating risk of poor product and process quality in the context of intended use of pharmaceutical products. Intended use, mitigation strategies sort of create the balance, brings a pragmatic perspective. I think I agree with Gerry. You can keep increasing the level of redundancy and so forth, but you

reach a limit, so you really need to have the right balance. And what is the right balance is the search that I think we will ask you to help us.

So the desired state is product quality and performance achieved and assured by design of effective and efficient manufacturing processes. Does that mean we don't have effective and efficient manufacturing processes today? We're not saying that. What we are saying is many products are effective and efficient today, some are not, but we don't have a means of judging which is which. We put everything in one basket and we regulate as if everything was the same. There's no difference in quality. So if you start distinguishing and letting science win, then there's a win that comes through.

I think what we don't do well is the second bullet. Product specifications based on a mechanistic understanding of how formulation and process factors impact product performance. The way we set specifications in absence of development data is to some degree guesswork. If these are your three batches that you tested in the clinic, this was your dissolution, this was the slowest dissolution, that's your specification. That's how we set specifications. And we do not bring into discussion and in our analysis what is the basis for that specification and how does that relate to process, how does that relate to

safety and efficacy. Often we go back to the historical. We needed a dissolution test, so we have a dissolution test. Whether the dissolution is rate-limiting or not, those questions sometimes don't come into discussion. So moving towards a mechanistic understanding of how or when specifications are set is important, and that cannot happen without sharing knowledge about your process understanding. And if you don't set your specification right, you essentially are throwing this over from R&D to manufacturing, and the manufacturing cannot manufacture it.

Continuous real-time assurance of quality. I think this brings in focus not only that we can be more efficient. This goes to the slide G.K. showed in terms of how much time is lost between the process and actually the analysis and all the time in between is not truly value added. Plus, doing a simple experiment takes much longer now than it should. So continuous real-time assurance of quality also brings in more efficiency in your R&D itself.

That's from a manufacturing perspective, but to make that happen from a regulatory sense, our regulatory policies should be tailored to recognize the level of scientific knowledge -- again, underscore knowledge -- supporting product application, process validation, and process capability. Today often I get involved in discussions saying that this is a validated process, but

the product is not capable. So what does that dichotomy tell me? If process validation doesn't lead to a capable process, what was the value of that validation? That becomes the question.

Risk-based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect quality and performance. I underscored "level of scientific understanding." So what is the right, appropriate level for that particular product and so forth. But this provides a win. You let science win with that bullet right there. Now, if you provide incentive for companies to do the right science and share the right science, then there is progress. I first then focus on companies that do not.

The capability of process control strategies to prevent or mitigate risk of producing a poor quality product. This is also important because today when we look at complexity, we would say aseptic manufacturing is a complex, high-risk process. So it is high-risk. That is a starting point for discussion. Then the question becomes how well understood is that process, how well controlled is that process, and so forth. So control strategies to mitigate or prevent risk need to be recognized too. Again, I think I'm reflecting what Gerry also said, the same thing. How do you manage your risk today?

We believe that since we articulated the desired state, not just dreamed it up -- this evolved from lots of discussion. Under the ACPS PAT Subcommittee, the Science Board discussion led to a common understanding of what the shared vision was. We have presented it at several public workshops and meeting. We believe it now represents a shared vision of the pharmaceutical community. It's not just what we are saying. I think this is what academia is saying. It's what industry is saying.

But I stopped there and posed this question to you. We believe these statements have become a shared vision for the future. Does the committee agree? I'd like to get your feedback on that.

Topics and setting priorities for discussion at future meetings. I think one of the most important topics is a common language definition so that we can continue our discussion more effectively, the definition of quality and risk, again risk in the context of what we are talking about, not redefining the word "risk" again. I don't mean that.

Risk models and management approaches. I think there are several models out there that I think we need to bring in for discussion, and we really would need this committee's help to do that. We will bring this back. I think David has a group working on this. I think each

working group within the GMP initiative, drug quality system, will have an impact on this, so we'll plan a whole committee meeting on this.

Manufacturing science and process understanding. Process understanding and control strategies for mitigating risk. I think the words are fine, but we need to flesh it out and actually define some working definitions and an approach for this.

Process validation and capability I think is a topic for discussion.

Manufacturing science and process understanding continued from the previous one. I just put everything under this right now.

Continuous improvement. Use of prior knowledge -- Bayesian approaches too -- for example, development data, for risk mitigation and justification of less burdensome reporting. For example, "make your own SUPAC" or "create your own SUPAC."

Design of experiments and failure mode analysis for assessing and mitigating risk. This is linked to the development. This is linked to how we set specifications and so forth.

Specifications and in-process controls. Interim and final specifications. I actually like better what Gerry mentioned, the life cycle of this. I think

that's a better way of looking at it. Risk- and mechanism-based approaches for doing this.

I will leave those thoughts with you. I think we really need your help to identify. I may have missed some of the topics, so you need to let us know what topics we need to do and how we want to bring them.

We did provide to you, hopefully in your background packet -- it's not in the handouts that were given at the meeting, but in your background packet you should have more detailed summary reports of the workshop. There were some very important points captured in that, especially on risk- and science-based. You have that in your background packet.

What I will suggest -- and I'll stop my presentation here -- is I think subcommittee membership here reflects very diverse backgrounds. It will help FDA and other subcommittee members if each member shares their individual perspective on the initiative and the proposed topics and the challenges they believe FDA will need to address before we get into subcommittee discussions and recommendations of the list of proposed topics for discussion. Clearly the objective that we have in mind today is these discussions will range from addressing specific questions posed by FDA working groups when they come back to you to addressing broader discussions of FDA

proposals. So when we come back to you, often we bring questions to you, but also we'll bring our proposals to you and we'll take your recommendations back to all the working groups under this committee.

So I will stop with that and hand it over to Judy.

DR. BOEHLERT: I think that Ajaz has outlined for us the discussion topics for the remainder of the day, starting on the second slide where he talks about the desired state and he's given us a lot of examples of what might be included in that desired state. I think the focus of this committee now should be on whether we agree with Ajaz's outline. Do we have suggestions for things that should be added? Do we want to change, perhaps, some of the things that have been put on the list? So I would open the committee to general discussion.

I had one issue. I've been sort of quiet letting all my committee members -- but I think there are some things that also may change in the future. You talked a little bit about specifications should reflect process capability. I think over the years on pharmaceutical products, we've set specs based on tradition, not on science. NSA on a dosage form is 90 to 110 and it's sort of traditional. It's not based on any process capability or anything of the sort.

I can envision a future where specifications will be set on process knowledge, that perhaps these traditional limits are still there in the compendia or whatever. Those are sort of the outlying limits, but in fact your process may have different limits.

I think that's something we need to think about because if you make a product and I make a product, we may have different process capabilities. Does that therefore lead to different specifications? And if it did, is there a public standard then that covers those? And how would that be addressed by the agency? Because process capabilities are going to differ manufacturer to manufacturer depending on what level you are in those pyramids and knowledge of your process and a lot of factors. So we're going to need to think about that, and I think the agency is going to need to think about how they might need to address that.

DR. HUSSAIN: I think at least the initial thought process for the discussion is I think the whole initiative, I think the PAT initiative as we started, we are not worried about the quality of products available today. It's the question of process understanding, improving efficiency and so forth. That was the basis for that.

So, for example, if you have a public standard

which says 90 to 110 and if your process is capable of doing a much narrower range, I think you're better off. Your process is more capable. But that does not mean that somebody who is less capable but still meets that standard is not safe and efficacious.

DR. BOEHLERT: And that's, indeed, the point that I'd like to make. They may both be fine standards, but the fact that his process is capable of 98 to 102 and mine is 90 to 110 doesn't preclude the acceptability of the 90 to 110 process.

DR. HUSSAIN: Correct.

At the same time, I think the thought process could be that since you have understood and controlled your variability so remarkably, then you understand your process better, so you would have less regulatory scrutiny than somebody who is reaching the limits with a highly variable product. So that's the approach, rewarding good science.

DR. BOEHLERT: I guess the fear on the part of industry always is if somebody does improve their process to the point that they can get to the 98 to 102, or whatever limits are very narrow, then indeed that does become the public standard. That's the "c" in current GMP and there's an expectation on the part of the agency that everybody meet that same standard.

DR. HUSSAIN: No. We understood that very

well, so that in fact the first question we posed to the Science Board was "c" in cGMP really has to be dealt with differently. So PAT, for example, is not a requirement. You don't have to do it.

But at the same time I think I really want to look toward the future. Today the clinical variability that we have, the development model that we have is, say, X right now. But as we go with pharmacogenomics, pharmacogenetics where we start targeting toward a more narrowly defined patient populations, that clinical variability may be different than what we have today. So I think we just want to be ready for the challenge also in the future.

DR. BOEHLERT: Gary.

DR. HOLLENBECK: Indeed, I wanted to follow up on the specifications discussion a bit. I guess I'd take exception with your comment earlier, Ajaz, about the current state of things relative to specifications because specifications have never been sufficient and meeting specifications has never been regarded as sufficient for the agency. It is for release of product on a routine basis, but if you make a post-approval change, for instance, you may still be held to higher additional requirements. So following up on Judy's point, that is one of the things that this discussion really need to focus on,

meaningful specifications, whether they're in-process or post-process.

DR. HUSSAIN: I think that's an important point. That's the reason we're calling it a drug quality system. You cannot discuss GMP without discussing specifications. That was the point I was trying to make.

MR. FAMULARE: Going to your point of in-process specifications, how much of that should be flexible in control of the firm in terms of optimizing their process as opposed to a specification that's a market standard. I think that goes to what Ajaz was saying about looking at least burdensome approaches or going back to Gerry's remark in terms of being able to have this life cycle type of a situation. In terms of optimizing the process as tight as it can be, that's to the firm's benefit. To the degree that cGMP is a minimum standard, that's even beyond that. So it's better to look at it in that sense as opposed to ratcheting up the "c" in cGMP.

DR. BOEHLERT: Tom and then G.K.

DR. LAYLOFF: I don't think ratcheting it up is going to improve quality treatment, clinical outcomes. With pharmacogenomics, I'm concerned that if you do identify those paths, are you going to try and titrate patients, which means that you'll have a multitude of dosage levels controlled between 98 and 102, or are you

going to keep the same thing that we have now which is economies of scale where you have maybe two dosage forms for treating the whole universe?

DR. HUSSAIN: I don't have any answers to that. I think we'll have to wait and see how that unfolds. But the only thing we know possibly is the variability structure that we have in the clinic could be different from what we have today.

DR. LAYLOFF: That may require a more critical titration of the dosages, which means that the PAT and economies of scale will not follow through.

DR. HUSSAIN: Actually the opposite. They will.

DR. LAYLOFF: Okay. They'll become more viable, essential.

DR. RAJU: I actually wanted to continue from where Gary left off and go back to the question of specifications and what does it mean and what is this whole process capability argument.

Specifications are supposed to be the voice of your customer. That's what, in terms of safety and efficacy, gets translated into specifications in your process. Those should not be changed based on your process or your process understanding because the voice of your customer for the bottom of the pyramid is still for safety

and efficacy. That does not change.

As you climb to the next level of the pyramid, you have a different customer. It could be a business customer. It could be the FDA customer. And you want to now, based on your process capability, maybe set control limits. That could be a basis of your negotiations for your internal customer for the business or maybe your understanding customer, maybe the FDA. But the basic specifications should not be changed based on the process. They can be changed but only based on what you are now learning from the customer in phase IV or as they're trying out more things.

We should not be changing specifications because we've been improving our processes. Our process capability goes up. We leverage that to make a deal with the regulator or with our business people. We should never change the specification for anybody else but the customer.

MR. FAMULARE: So that our level of scrutiny on specifications should be established based on the safety and efficacy and stay right there.

DR. RAJU: Yes.

MR. FAMULARE: Then in terms of process, process capability, and so forth, that's in terms of --

DR. RAJU: Control limits or capabilities.

MR. FAMULARE: -- control limits, inspection,

and those types of issues.

DR. BOEHLERT: Go ahead. We're scheduled to take a break at about 3 o'clock, but I don't want to interrupt in the middle of a sequence here.

DR. HUSSAIN: I think I agree with Joe, and I will just build on that. I think what happens then, as the development programs emerge, your customer voice essentially is the safety and efficacy database that sort of defines what the broad specifications are, and they essentially become our public standards.

Now, if you keep improving your processes to become more and more capable, then I think the benefit comes, as G.K. said, in terms of regulatory relief because now it's a low-risk situation.

DR. BOEHLERT: I think I would agree with G.K., that it's process control you're talking about, not final specifications.

A few more and then we'll take our break.

DR. HOLLENBECK: I would just point out that I don't think our specifications have necessarily been developed that way. I think you're giving them too much credibility in many cases. They are just things that we do. They're often not related to any quality attribute to the dosage form at all. I think that's some of the win part of the win-win that Ajaz talked about.

DR. RAJU: Just kind of taking off from that, that is a very key point. If we agree -- and we should because this is a discipline that comes from every place on the planet -- that the specifications are about the voice of the customer, we have to now challenge our practices of how we define our specifications in that context because I've seen in many situations when, let's say, we have a 6 sigma process and so we don't have too many investigations, we still set our specifications to be at 3 sigma so that we always have a few investigations so that we demonstrate that we investigate.

And I've heard many cases of people coming in from their own company's quality side or from the external investigators where they say that if you have a very wide specification, that's not a good thing. If you're very capable, it could work backwards on you.

So the key isn't theory. It's the voice of the customer and it should not change. It should be changed based on the better understanding of the voice of the customer.

But in practice, we have the self-fulfilling prophecy. It's because we have an asymmetry in the knowledge we get from our customer because there are so few people and so difficult to measure, that we've ended up having our specifications being set by the process which is

creating a real chicken and egg problem. I think we have to go back to the customer and change the specifications based on the customer, and we've got to do better than that. It's not perfect, but we've got to create an internal business, a regulatory benefit for the next level and try to see them separate, although it's very difficult in this industry, but it's very difficult in most other industries too.

DR. BOEHLERT: Nozer, did you have something you wanted to do before the break?

DR. SINGPURWALLA: I'd rather do it because then I want to leave.

(Laughter.)

DR. BOEHLERT: Okay, by all means then.

DR. SINGPURWALLA: Ajaz gave a very nice presentation. If I was a student, I would give him an A plus, but I'm going to just reverse the role now. You asked us to give individual perspectives on the initiative.

My assessment is that your heart is in the right place and your head is getting there.

(Laughter.)

DR. SINGPURWALLA: You covered all the technologies quite nicely and the big challenge you asked is how to apply these things.

The second comment I want to make is that risk

analysis is fundamentally a mathematical endeavor involving fault trees, prior information, fusing information, experimental design, eliciting expert testimonies, probability calculations, control theory, time series analysis, and I'll throw in econometrics even though I don't think much of econometrics.

The question is, is this community ready to bite that particular bullet? Are you prepared to invest the time and effort it takes to understand this whole technology before you want to apply it? I think there's going to be a process of education.

There is the question of defining quality and defining risk. Yes, we should talk about it, but I think these matters should be dismissed very quickly. And the risk models and management approaches and how to put all this to work is where the challenge lies, and that is where I think we should focus and not try to reinvent the wheel because you'll be an isolated community.

Thank you.

DR. BOEHLERT: Nozer, thank you very much for your contributions today. We really appreciate your input.

I would remind the committee that we got started on some really good discussions here. They should not continue through the break. Hold off on the discussions and we will continue again when we reconvene

about 3:20.

(Recess.)

DR. BOEHLERT: I hope we didn't lose our initiative for discussion when we took our break. Well, yes, Nozer is gone.

(Laughter.)

DR. BOEHLERT: But I think he managed to get a few last comments in. We thank him for his participation.

I'd like to open the discussion up further to the committee. If you look at Ajaz's slide number 2, he talked about the desired state, identify and prioritize topics for discussion, and recommend format and background information FDA should prepare for discussion of identified topics. I'd like you to take a look at those and address those, if you might.

Have we talked enough about the desired state? Ajaz, have you gotten the information you need from us?

DR. HUSSAIN: I have but I think Gary wants to change it. No, just kidding.

DR. HOLLENBECK: I don't know if I want to change anything, but let me throw a couple of things out.

We talked a lot about risk. I guess traditionally we think about risk in terms of the active or in terms of a therapeutic outcome. Certainly the barometer for risk assessment in the SUPAC initiative was based on

the active. We looked at therapeutic index. We looked at solubility and permeability.

Now in Gerry's slide, there is this new barometer of manufacturing science. Are you anticipating that one will replace the other, or do you still think there will be a preeminent emphasis on the drug?

DR. HUSSAIN: I think, in my mind at least, the systems will evolve in a more comprehensive and systematic way. I think SUPAC looked at one piece of the thing, and just looking at one piece of the thing, you never achieve what you are trying to achieve. I think you have to look at it from an entire quality systems perspective.

You raised the issue before, specifications do not tell the whole story. I think there are dramatic examples of that. In the mechanical industry sector, for example, Ford versus Mazda transmissions. The same specifications and different reliability and so forth. So there is value to that. And in a multifactorial system, just meeting specification would mean that you might be on edges on different parts of the different specifications, and truly in a collective way, that really doesn't tell the whole story. I think that was the debate that we had in FDAMA and the SUPAC. Specifications do not tell the whole story and process is important. So I think you will see a merger of the two concepts in a whole systematic way.

DR. SHEK: With regard to this bullet, specifications based on mechanistic understanding of how formulation and process factors impact on the product performance, I would assume there is some kind of a situational limits. And I don't want to take the car example. For performance of a car, you need, I assume, four wheels, a steering, an engine, transmission, a battery, and if you want to stop, some brakes. Right? But you can have a BMW or you can have another car. Now, both of them are going to bring you from A to B and function. If you are developing two products maybe for the same purpose but being made in two different processes, you might come out with different relationships. The question is where do you stop, and is one of them being chosen or both of them can be used for specification justification?

DR. HUSSAIN: From an FDA perspective, I think what we do is we define the minimal standards, whether it's the CMC review or GMP. These are the minimal standards. If something is acceptable from that perspective, and essentially the determination is this is safe and efficacious for use, that's what it is.

If you use the analogy for a car, in that analogy it's actually easier to determine whether one is better than the other or not. We can look at how many times the car has to be in the shop and this and that and

so forth, but in a clinical setting that's not easy. So the safety and efficacy is the starting point and that's the foundation on which you have to base that. Then I think the manufacturing process provides a means for minimizing the risk of poor process quality, and I think that's the angle that we wanted to bring in.

DR. SHEK: But what will be the standard for this product? We talked at the break about the evolution of technology and capabilities. We talked about analytical areas. You have the factors and you had columns and one drove the other with regard to sensitivity, and to some extent I believe and I hope that we will see those and the manufacturing sciences will have tools today that they can measure something. And the limit will be the tools that we can measure, and then we'll have a process, I would assume, which will now overpass the detection system that we have. The question is, in this case will the safety and efficacy will be the baseline or if I'm improving on my product, will that not become the standard for other products?

DR. HUSSAIN: I'm not sure I got that.

DR. LAYLOFF: I wanted to go back to what G.K. said. The client is the patient and safety and efficacy is all there is. Now, I don't think any company would use 90 to 110 as a release specification, would they? If you intend for your product, throughout the course of its life

cycle, to meet 90 to 110, if you release at 90 to 110, you're asking for trouble. So your release should be significantly better than that so that your product throughout the life cycle or any group of 10 tablets will meet that 90 to 110, which means statistically you have to be narrower than that.

DR. SHEK: Yes, I'm not talking about the 90 to 110. I'm having 95 to 105, and then I can find that I can make 97 to 103. It's to some extent what Gerry was talking about, the life cycle. Now, where will be the standard for this product? Do we always go back and say if 90 to 110 satisfied them --

DR. HUSSAIN: I think you're missing the point here. The point simply is that as an approval decision, we said that suppose the specification that was the basis for approval was 90 to 110 and that will then throw to exactly what Tom said, is if you don't meet that, you recall that or you don't release that batch. But to manufacture that in a consistent, reliable, reproducible way, you cannot have that as your release specification. Some companies may have much more variability and may be prone to more failures. Therefore, the variability would be a reason to consider them high risk. Companies which meet a much finer one as an internal one would be low risk. That's the way we look at it.

DR. DeLUCA: I guess I have a little problem with this. If at 90 to 110 percent you have a safe and efficacious product, I don't think meeting a pharmacological outcome should deter one from trying to improve the product from a manufacturing standpoint. That shouldn't be the end. We've accomplished a pharmacological effect. We don't have to improve the product any more.

I think we should be striving to make improvements in the product. And it seems to me, from the standpoint of specifications, those specifications should be what the process is able to provide. If 90 to 110 percent is fine pharmacologically, that doesn't mean if you're capable of producing that at 98 to 102, that you should have 90 to 110 as your spec. I think your spec should be tighter.

DR. LAYLOFF: I disagree with that, and I hate to end up on this fence. When we get to that curve that Gerry talked about, if you keep improving the quality, you can continue to, but the investment doesn't improve the quality of the product in terms of therapeutic effect. So you're really not improving the product in terms of the patient application. You're intellectually improving it, which is increasing the cost which is reducing availability, and I think that's a critical factor. You can talk about purifying a drug substance down to 99.999

for your mass production, but you drive the cost up, and you don't improve the therapeutic outcome. Now, is it useful to drive up the quality of product and cost without an improved therapeutic outcome? And I don't think it's valid.

DR. DeLUCA: How do you know you haven't improved the therapeutic outcome?

DR. LAYLOFF: Because you established that in the clinical studies.

DR. DeLUCA: Yes, but you may improve a process -- there may be things that you haven't tested. There are a lot of products on the market that after five-six years, they find things wrong with them.

DR. LAYLOFF: Right.

DR. DeLUCA: Okay, then why didn't they find it out in the clinical testing? They found it out after a lot of use. I'm not saying there are no benefits pharmacologically. What I'm saying is that once you have achieved the pharmacological outcome, that shouldn't be a deterrent to not to improve the process from a manufacturing standpoint.

DR. LAYLOFF: I think you should improve the process to reduce well-time, to reduce cost, because reduced cost is improved availability. I think that's the only rationale for doing it. You're reducing costs of

manufacture which improves availability, which I think is important.

DR. BOEHLERT: I would add there are other reasons to improve the process as well and those are if you're getting OOS, out-of-spec, results or aberrant out-of-trend results and things of this sort, you're wasting a lot of time on investigations, where if you improve the process, you would save that time, reduce cycle times because investigations drive up cycle times tremendously. While you still have that same specification limit, you've reduced the variability in your process.

DR. LAYLOFF: You've reduced the cost of production.

DR. BOEHLERT: Absolutely, yes.

DR. LAYLOFF: And I think that's a very worthwhile endeavor.

DR. BOEHLERT: So there are lots of reasons to improve the process without changing the specifications or having an impact on changing.

DR. PECK: There are still those items, however -- not many of them -- that have narrow therapeutic windows, and I think we always have to be attentive to that particular situation. Some people have tried to forget that. Many of them are low-dose drugs. Now the process becomes extremely important as far as those particular drug

substances. And we are concerned about the patient, the customer that we are dealing with. So we can't forget that.

The other thing is the interchangeability. I will pick out one particular device, a mixer. We have specifications on products, but I think we need to look closer at some of our devices to see where they fit in in our particular process. That can be significant also.

DR. BOEHLERT: I think there are also products that have many different strengths within the product line to the point where if your specifications are too wide, they actually overlap, so that in fact you could release two different strengths at the same number and be within specifications. But I don't know what the answer to that is.

DR. HUSSAIN: I think this has been a very valuable discussion sort of building on what Pat talked about. One of the challenges and one of the reasons why this industry, especially in the manufacturing sector, has become stagnant is that thought process in terms of if you improve, the only option is you get tighter and tighter and tighter specifications. And that actually is a big hurdle for continuous improvement in this.

Now, I think that itself is a major topic for discussion. I'm not sure that is for this committee. I

think it's more for the clinical folks. We have to have that discussion.

But the point here is this. If you talk about science-based specification setting, now what is the most logical way of looking at that? We have humongous clinical trials that are designed to essentially establish safety and efficacy. Yes, they will not cover every patient population, and yes, they will not cover every patient. But that is the standard today.

So if we approach specification setting saying that if you improve your process, you have to tighten the specification, first of all, there's no incentive for doing that. Secondly, what is the scientific basis for that? Yes, tightening is better, but on what basis is it better? Because I think just the variability and the time of how you take the drugs and so forth really defeats that purpose.

I think we really need to think about that very carefully because I think in principle what we say is the tighter the specification, the better. I agree with that, but the question comes back to on what basis.

I also have referred to an encounter I had with our traditional specification. I was at a meeting in Tennessee and giving a lecture. I said if the content uniformity is 85 to 115, and they just started the stage

one, and somebody from the audience came up. He was in the paint industry. He said, you mean to tell me it's 85 to 115? Our formulations are far more complex. We have a tolerance of 1 to 1.5 percent. So I just kept my mouth shut.

(Laughter.)

DR. HUSSAIN: But again, the intended use is what comes back. When you have a paint, visually you can distinguish whether the content is more than 2 percent off. So there is a requirement for the intended use. You really need to have that. I think, yes, for intended use we need to define that. If it's a narrow therapeutic index drug, the specification setting at the approval process should account for that and it sort of needs to define that at that point.

DR. LAYLOFF: I think also you're looking at comparing quality in suspensions as compared to heterogeneous compressed solids.

DR. HUSSAIN: Suspensions are more complex.

DR. LAYLOFF: Not when you have to stir before you use them.

DR. HUSSAIN: Judy, let me go back to Efraim, sort of reflecting back. What do I mean by mechanistic basis for establishment of specifications? Let me build sort of an example on that. And I'll take a very simple

example of an ICH Q6A decision tree and how do you set specifications for dissolution.

Now, for an immediate release dosage form, as you look at what are the acceptance criteria that you define, one of the questions is, is the drug highly soluble? If the answer is yes, then the question that is being asked is, is the dosage form rapidly dissolving? If the answer is yes, the ICH Q6A decision tree allows you to move toward a disintegration test as a means for that when you establish a relationship disintegration and dissolution.

I have a fundamental problem with that because you're comparing two different test methods, but the principle I think is right. If you know what the mechanism is -- for example, in your studies you have documented that dissolution is not rate limiting. You have a related bioavailability study that shows solution and tablets are essentially superimposable in the blood-concentration time curve, so dissolution is not rate limiting. So why would we want to set a dissolution specification is a logical question to ask. And we don't ask that question today.

So that's what I think is an example of getting to the mechanistic basis of what is the mechanism of absorption. Is it rate limiting? Is dissolution becoming rate limiting? I think we need to get that discussion

going before we automatically say we need a dissolution specification or not. That's what I was trying to say.

DR. BOEHLERT: Other comments? I would just add to the dissolution, it also has to be a meaningful dissolution test. I've seen dissolution tests imposed. You must have a dissolution test even if it's in 0.1 N sodium hydroxide, which at least one is. And I'm not sure what the relevance of that is, but it's the only thing that dissolves the drug, so there's a dissolution test.

DR. LAYLOFF: That's for caterpillars. Caterpillars have a very basic gut.

DR. BOEHLERT: Oh, now I understand.

(Laughter.)

DR. BOEHLERT: Other discussion comments?

DR. LAYLOFF: I'll put a hypothetical here. I think one of the things that you're trying to accomplish is to encourage the industry to use new equipment. Right now I think you can legitimately argue there are disincentives to doing that.

So are you envisioning a situation where I could replace a mixer or maybe a whole series of unit operations with a new "phenozerator" that does all of these things and I can take out my old stuff and plug this thing in and whatever in-process controls I have in place will be sufficient to determine whether the process has changed the

outcome?

DR. HUSSAIN: No. I think you have to look at it from this perspective. Let's stay with immediate-release conventional tablets as an example.

Now, let me step back before I answer your question. One of the products I did, after we had completed the University of Maryland research project, for example, is to take the University of Maryland database on the formulation changes that we had and so forth for the six different drugs that we had. I said, now that I have a designed experiment here, I know what is critical and so forth. Can I use that to learn and predict what the behavior of submission data is? I think we actually did this study.

So, for example, for metoprolol tablets, the experimental formulation that we had at the University of Maryland and the scale-up and all that, we used that data and developed a model to predict the dissolution behavior of data in our submissions. So we have about 9 or 10 generic formulations and innovator formulations. We had about 11. So we could actually predict nine of them on the dot. Two of them we could not predict well.

But what that told me was you have slightly different compositions, different unit operations. Literally everything is different in these formulations.

Yet, I think all are bioavailable, all meet the shelf life, and dissolution was sort of a signal. So essentially the system works in the sense you can have big differences in formulation and processes, yet you can have the same safe and effective product. That's essentially what it is.

Now, each of those formulations came about from different starting points. So it is quite possible to come up with a safe and efficacious product from different ways that is bioavailable, that meets the shelf life and so forth.

Now, if you have process understanding and so forth, how do these factors affect my shelf life or stability and bioavailability? So if you know what the factors are and how they impact, then changes should be easier to manage. That's what I was trying to get at.

DR. HOLLENBECK: I guess my point is, how do you have process information on a process you've never used before or one that didn't even exist when you were developing your product? And the reason to ask that question is if there's no way to do this, if there's no way to substitute in your new piece of equipment without invoking the existing strategy, then why do it?

DR. HUSSAIN: I think it would be ludicrous to do something without knowing what you're doing.

DR. HOLLENBECK: Well, that gets back to my

original question.

DR. LAYLOFF: But we've always held as an anchor like the pivotal lot. That's been sort of the anchor that you hang onto. The content uniformity, the assay, the dissolution of the pivotal lot is what you hang all the safety and efficacy data on. You say anything that you do you come back to that, which is why you say dissolution is important because it relates you back to the pivotal lot.

Now, if you want to change that, then you have to go back and redo the pivotal lot, and I don't think that's reasonable. I think you can change production, but you relate everything back to the performance of that pivotal lot. So you define it very carefully so you have that anchor on which to hang changes. Otherwise, you end up in a safety and efficacy study again.

DR. HUSSAIN: I'm losing track. I've lost the chain of thought here. I'm not sure what the discussion --

DR. HOLLENBECK: You're probably not the only one.

(Laughter.)

DR. HOLLENBECK: I think Tom is referring to post-process testing. The pivotal lot is characterized primarily by a dissolution test. We're envisioning a new era. Products are released by in-process testing. My

question is, I've got a brand new piece of equipment that will do multiple unit operations. I want to plug it in because I want better products, I want to do all the things that you want me to do. Yet, as I understand it, I'll still have to do a biostudy or something to prove that I have equivalence.

DR. HUSSAIN: Well, I think if it's a black box, in the current paradigm I think the answer is yes because we don't know what the system will behave like and so forth.

But, for example, if you can imagine a future where we have understood the attributes of in-process materials as it relates to, say, end product performance. To accomplish that, you will have to move away from the current types of controls to process endpoints. For example, you will blend until it's homogeneous, so you have an acceptance criteria which is independent of -- it defines the acceptable variability in the blend itself. Then if you have to granulate, you'll granulate to a size and porosity of something that actually reestablishes similarity to dissolutions. So you'll have to move in that. We're not there yet, but that's what will need to happen to get to that stage.

DR. HOLLENBECK: And that's exactly the answer I wanted to hear. That's quite a change from the agency's

perspective because I recall process being a critical consideration during SUPAC. We've had that whole table full of excipient changes, often large percentages, but a minor change in a process really sort of caused concern. So that ought to be one of the working groups here really focusing on those in-process tests that can identify the attributes that you want of a blend of a granulation and of a tablet independent of how they were made.

DR. HUSSAIN: I agree, but I think reflecting back on that experience, since that was my start of my career at FDA and working with you guys, my read was one of the things that created that discussion and -- the concern was lack of process understanding within the agency, especially in the review chemists because they really did not have that information to evaluate and so forth. So that was a complete black box to them. So a minor change might have a dramatic effect. That was the concern that was coming out again and again.

So in this paradigm, I think from a systems perspective, you really have to bring that information into the decision making process. Then only we can move forward. Otherwise the same system will continue.

MR. FAMULARE: So you would take the most -- I don't want to use the word "onerous" but the most conservative approach based on your lack of knowledge. So

it goes back to the slide that Gerry presented, aside from the defects that were pointed out about it.

(Laughter.)

MR. FAMULARE: But if you go back to that slide, as you increase your knowledge, the amount of information that you would need to file would be less. Again, the real basis would be, on a risk-based, the safety and efficacy data.

DR. HUSSAIN: Right.

I think just to sort of build an example here, we just completed a study, but I think we wanted to look at magnesium stearate as an example. If you recall the SUPAC -- I don't think I can recall the exact percentage number, but at level 2, component and composition change, I think a .2 percent change in magnesium stearate is a level 2 change. Maybe that's not the exact number. Now, we did not allow that change to occur for narrow therapeutic index drugs. We did not allow that change to occur for class 4 drugs, say, for furosemide, BCS class 4 drugs.

Now, we know magnesium stearate is important for dissolution and other things, and we have known that for 35 years. We actually have known the mechanism of how that thing happens for a long time.

But at the same time, what I would argue is there are formulation strategies that can negate completely

the undesirable effects of magnesium stearate. In certain formulations, you can formulate the product to be so robust that it will not be affected by how much mixing you do and if you have more magnesium stearate or not. Today we do not recognize that science at all in our decision making.

So that's what I want to say because at least in 1977 we knew this, that if you include about .01 percent of sodium lauryl sulfate, you can actually overcome the hydrophobic nature of magnesium stearate on dissolution. But we don't use that knowledge today in decision making. We say magnesium stearate was implicated in dissolution failure, so it is applicable across the board. So that's the example I wanted to show.

DR. DeLUCA: I guess what you're talking about, though, was you're doing mechanistic studies here and moving up the pyramid there or up the scale in Gerry's. So you're gaining knowledge to make those processing changes, and I see that.

I guess what I understood Gary to say here is without gaining any knowledge, just putting in a new piece of equipment and getting the same thing, if you then meet the same specs that you've set with that new piece of equipment, doesn't that fall into here, what Helen pointed out in one of her slides, changes without prior approval?

DR. HUSSAIN: Right. But I think that becomes

a basis -- and you'll hear about it tomorrow -- of a comparability protocol that defines and that shares the knowledge. In the absence of that knowledge, there's no change in our system. You have a prior approval supplement. You probably have a biostudy. You have three batches of stability. Without that knowledge, we're not changing. That's it.

DR. BOEHLERT: Other comments? Gentlemen on this side who have been quiet, no comments? Not right now. That's fine.

Efraim.

DR. SHEK: I don't know whether we got stuck on specifications, but we are talking now about knowledge and it came across quite a few times. And that's also connected to the development of pharmaceutics. We are talking about we are transferring -- we assumed the industry or the applicant is transferring a regulatory document, but at the same time we are trying to transfer knowledge. It's very similar maybe to technology transfer. It's not only the tech transfer. You have to transfer the knowledge that you gain for somebody who is going to use it.

Maybe that goes a little bit back to the stick and carrot I was talking about in the morning because that can become another, let's say, regulatory hurdle because

it's more information where the dilemma will not be transferring knowledge, but arguing whether it was done the right way. And then we'll have different perspectives. At least from my part, it would be nice if we have a system. This is a transfer of knowledge. That's an explanation, a rationale for how this product was developed. And that should help. It shouldn't prevent. And the question is how we will build a system, at least from perspective --

DR. HUSSAIN: That's the reason we have advisory committees, to seek advice.

(Laughter.)

DR. SHEK: So my advice is use it as a knowledge transfer not as a regulatory hurdle.

DR. HUSSAIN: But what we will do is, when we bring the topic up for discussion, clearly we'll come up with a proposal and we'll seek your advice and input on how to do that. But I think I have learned through the PAT process is the "don't use/don't tell" approach. In a sense this is the "don't tell" approach. If there's anything I have learned from the PAT experience, right now I'm scrambling to get the team together because the flow of submissions have started coming in before we even have a guidance.

So I think the question of trust and so forth essentially is if you don't require this and if we can

simply focus our discussion on science, these things get resolved. That's the way I'm thinking right now.

But the reason for the advisory committee is to seek your advice and input on those critical questions that you are asking me today.

DR. BOEHLERT: Ajaz, have we addressed the issues that you need us to address today, or is there something that we haven't touched on that you would like us to?

DR. HUSSAIN: Maybe for the next three or four meetings that we will have with you, I think there are key topics that we would like to bring to you. David's group is getting ready with a potential discussion on risk, quality, and so forth, but I think that has to be approached by every working group. That needs to be honed in, defined, and at least build consensus on the words we use to describe this so that the rest of the discussion can happen more smoothly. So the first topic probably for the subcommittee discussion could be terminology or whatever you want to call that, defining what we mean by quality, risk management, and so forth. It would be one of the first topics that we discuss with you.

Then following that I think there are a number of things we really need to seek your help on. Process understanding. What is the level of process understanding

and how do we link it to risk or what are the metrics for process understanding? Is process capability a metric for process understanding? All those things.

So what I have done for you is listed some of those topics that we are actually discussing internally and working on and wanted your sense of what is the right sequence of discussion topics from your perspective and how do we structure that discussion that will be more effective from your perspective. If we can get that feedback, I would appreciate that.

DR. BOEHLERT: Feedback?

DR. HOLLENBECK: Well, I'd give you feedback on page 5 of your handout, the desired state slide. You asked what the committee thought of that. As a member of the committee, I like that. I think that's a well-stated objective.

DR. BOEHLERT: Other comments or thoughts?

MR. PHILLIPS: I just have a question. On page 5, the first slide on page 5, product quality and performance. Was there a reason we left product quality and safety off?

DR. HUSSAIN: Quality is the foundation for safety.

MR. PHILLIPS: I think it is.

DR. HUSSAIN: That's the way to interpret that.

MR. PHILLIPS: I don't see a problem with it. I would probably add it in.

DR. HUSSAIN: Because the way I approach this is in a sense if you don't have quality, you cannot make safety and efficacy decisions. That's the foundation you have to build on.

DR. BOEHLERT: Was somebody else going to make a point?

MR. PHILLIPS: Aside from that, I like those slides on page 5.

DR. BOEHLERT: I think what you're hearing is lack of disagreement with what you presented.

DR. HUSSAIN: So the point is proven. It is a shared vision.

DR. BOEHLERT: This has been a very interactive group and suddenly they've run out of anything new.

DR. HUSSAIN: If the committee would go through the list of topics and the sequence, if we can agree on the sequence of discussion. I don't promise that we'll bring all of them to this.

DR. BOEHLERT: Is that page 6?

DR. HUSSAIN: Starting on page 6. And if we identify the topics for the next meeting, keeping in mind you have tomorrow's discussion that will discuss change and so forth, if you could help us how you would like us to

prepare in terms of what type of background information would be helpful for you, how should we structure the discussion.

I heard this morning a model which seems attractive to me. I don't have that information. G.K. mentioned that. Nozer mentioned that. That was the DOD approach. If we could get some discussion on that, would that be a framework for maybe a subsequent discussion? If we could get some input on all those aspects and topics that we may not have listed and you think would be important for discussion.

DR. BOEHLERT: Any comments from committee members?

DR. DeLUCA: On that first, the definition of quality and risk, we started talking about risk. We talked about risk quite a bit this morning and used a definition of it. When we talk about risk, just focusing on loss of safety, efficacy, and economics? How far do we go on that?

MR. HOROWITZ: That's the question. What is the harm or what is the loss that we want to focus on? Depending on how we define that, I think it will have very different applications. Our preliminary thinking on this and the emerging consensus seems to be that the focus seems to be emerging on safety and effectiveness and reductions in quality of the drug that impact safety and

effectiveness.

Now, that doesn't mean that there aren't other reasons, other customers, and other objectives to further improve and tighten up quality. But for our regulatory purposes, our definition of quality might be different than the definition that's used inside the manufacturing facility where they're thinking not just about the safety and effectiveness of the drug, but they're also thinking about how to most efficiently manufacture the product. And they may want, for example, a margin of safety. Maybe that's not the right word. A margin that would ensure consistency that would be even greater than we would want for safety and effectiveness considerations.

But I think that's what we want to come back to the group with. We want to do some more thinking. We want you to hear what Gregg Claycamp has to say tomorrow about applying risk concepts and come back with a more detailed and thorough discussion on the subject. But, of course, we're interested in preliminary thoughts that you may have today as well.

DR. DeLUCA: These risks could be perceived as well as real, and the only way you know that they're real is you have to do some investigation. So the question is do you proceed to try to reduce these or prevent these things without that kind of information. You just perceive

that there's going to be a loss of safety or efficacy, and you proceed on that basis with trying to reduce the perceived risk. These are questions too.

DR. BOEHLERT: And I think it came out of the discussion earlier today that the application of that risk is what we need to focus on, not necessarily the definition, because those are fairly well known, but just how was that going to be applied. I think that's something -- I'm not speaking for the committee -- that we're all interested in. I see nods.

DR. HUSSAIN: There's a classical dichotomy in terms of setting specifications. When we say quality is the foundation to make safety and efficacy decisions, then if it's safety and efficacy that defines specifications, that's the circular argument that we often get into.

I think the process by which a company develops the clinical trial material -- because keep in mind they're investing significant resources in doing the pivotal clinical trials and so forth -- the design aspect, knowing the drug, knowing the intended purpose, knowing the intended population, the thought process that goes into designing your clinical trial material that yields the safety and efficacy database, I think that sequence of thought is often not considered when we set specifications internally. I think that is an important point that we

need to probably discuss also.

DR. BOEHLERT: You said something with regard to safety and efficacy, and safety and efficacy in setting specifications is not always the issue. Very often it's not. If you set limits on impurities, for example, they may be more based on process capability and what you actually see rather than on safety. You may be able to demonstrate that 5 percent is safe, but if you only find .2 percent, you're not likely to set a spec at 5. So there are a number of issues here that need to be considered. So we need to be careful in defining something in a manner that may not apply.

DR. HUSSAIN: Within the context of SUPAC -- tomorrow in my presentation I have some slides on risk management, the SUPAC model sort of a thing. There I think the risk that we define is risk to quality in terms of having a different shelf life after a change or having a different bioavailability. So the SUPAC structure was designed to minimize those risks so that we assure the same shelf life or better shelf life and bioequivalence between pre- and post-change models. And we use that as a model for SUPAC. So the criteria there essentially then became the bioequivalence standards, 80 to 125, and then the shelf life itself became the decision making point.

DR. BOEHLERT: But a change in the shelf life

is not necessarily bad. That's a business decision perhaps. You don't want one that's six months, but whether it's three years or four years may not matter.

DR. HUSSAIN: No. But the shelf life reflected on the label should be accurate. That becomes the basis for that.

DR. BOEHLERT: Yes.

DR. HOLLENBECK: I guess I'm looking at the third bullet now, the manufacturing science and process understanding. I've sort of been reflecting on the catch 22 that we always have in these situations. The repository of this information is in the industry, and justifiably, if you've invested in better processes and better understanding, it gives you a competitive advantage that you may not want to share with the world. How are we going to get this information in the public domain so that there can be a broader way to take advantage of it?

DR. HUSSAIN: Well, I don't have a solution for public domain, but I do have a solution for utilizing that information effectively at least for that company. The SUPAC guidance, for example, had to be very broad, somewhat superficial in terms of what we could do because we could not get deep into each product and each formulation type and so forth. But the comparability protocol or "make your own SUPAC" concept allows a company, if it has this

information and knowledge, to share and take advantage of that in a private way, but it does not bring that into the public domain. That is sort of a different challenge probably not within the scope of what we are doing here. I think we need to take that up in a consortium type of a scenario.

DR. BOEHLERT: Tom, you look like you're about to say something.

DR. LAYLOFF: I was. I was thinking about what Gary said about substituting a blender in maybe some functional process. I was wondering if that is a significant issue for a heterogeneous solid state compression on the same scale as changing an excipient by plus or minus 20 percent. I don't think so. I think allowing a change of plus or minus 20 percent is far more drastic than changing a blender or something else along the stream in terms of product quality issues, and they allow that.

DR. DeLUCA: But you could probably run some tests, Tom, pretty quickly that would give you a better feel for that too to get some information.

DR. SHEK: You will be surprised about the efficiency of different mixers or granulators and a plus/minus 20 percent of excipients might be minimal. But there should be a way to test for it because what you do,

you just show that the product that you get is the same product. You might have to change your parameters that you're using, and that's basically one of the issues that we are struggling with. As you scale up and so on, you are switching, there are differences. But again, if we know how to test it, whether it's the PAT or another one, I think that becomes, to my understanding, a nonissue.

DR. LAYLOFF: I think PAT is a way of assessing homogeneity. You're looking at homogeneity of process, and if you change blenders or whatever, you're still going to be assessing homogeneity, and I think homogeneity is a reasonable endpoint, but I think again a 20 percent change in excipients is a more startling thing to do to a product.

DR. BOEHLERT: Aren't the PAT concepts also being used to test for performance parameters, to look at those functions of the product that will impact performance using acoustical technologies and things that we don't use today? So it's possible that a technique like that might be able to tell you that if you changed to this blender and eliminate a whole number unit steps, you do preserve the integrity of the product.

DR. PECK: I think PAT is going to be the answer to our ability to change certain pieces of processing equipment. We've demonstrated this already, and we feel strongly about it. I think that's going to be our

key to more flexibility in processing.

DR. BOEHLERT: Joe?

MR. PHILLIPS: I just want to comment on the change of equipment. We were faced with this same challenge when we first got into the SUPAC domain. FDA came out with a statement that if you use a similar piece of equipment, you got certain regulatory relief in the filings.

The first thing FDA had to do was define what is similar. I think they had something like 250 questions in the first week, what is similar? We ultimately went to ISPE, the International Society of Pharmaceutical Engineers, and said, can you make us a list of what is similar equipment? Can you tell us a blender is a blender is a blender? And they took that upon themselves, on a volunteer basis, put about 60 engineers on the project, and in a matter of a few months, came up with a list, which is now FDA's list of similar equipment.

And it was based on two principles: engineering design and operating principle. If it had the same in those two cases, then it was a similar piece of equipment. If it was a different operating design, it was different and it fell out of the SUPAC domain. It had to be considered in other domains.

DR. HUSSAIN: I think the SUPAC development

experience was very valuable, let me put it that way. The equipment addendum was actually an afterthought. We scrambled to get that done.

But at the same time, I think the challenge that we face in the future is very different. To give you an example on that list, we do not distinguish encapsulator machines, all in the same category. Now, you go from a Zanasi to a Genkay -- this is the Ph.D. thesis at the University of Maryland, and we just looked at that -- then the challenges come. One is a dosing disc, one is a dosator type. I think you run into an interaction between formulations and so forth. It's not as straightforward.

I think SUPAC worked from one perspective as a broad general guidance. In the future, what you're looking at, if you want to recognize the level of science, it cannot be a general guidance. It cannot be a general SUPAC and so forth. The guidance would be more principles rather than if this it, do this. So I think that's the model we have to move towards.

Now, that opens the challenge of consistency. Keep in mind one of the driving forces for SUPAC was consistency across review divisions, but as we go towards more science-based principles-driven guidance, the challenge would be maintaining consistency, and that has to come in through training, certification programs, and so

forth.

So we didn't have training and certification programs from that perspective for SUPAC. It was getting the consistency done. We did that. Now the next evolution in this process is more science-based that the company can bring different levels of science to justify different changes, so it's a custom SUPAC, and the consistency will have to come from the ability of our inspectors and our reviewers to recognize and do good scientific assessment of that information. So you're looking at those two principles coming in.

DR. PECK: There are individuals currently who are trying to model certain unit operations, and there have been some encouraging results about the modeling and trying to associate either the mechanistic part of the process and then also relating sort of in-process controls that are necessary for it. We're seeing this bit of light on modeling of processing in the pharmaceutical field. Others have done it and it's time that we took a look at this approach to process evaluation.

DR. GOLD: Ajaz, one of the things I've been wrestling with this afternoon is the issue you just raised, and that is, in the past we've given our reviewers very defined guidance or guidelines, if you will. SUPAC is very clear, what's permitted and what's not permitted.

For years I've heard complaints from regulatory people about inconsistency in the review divisions. Different divisions have different standards and information requirements are very differently accepted by the different divisions.

Now, if we get into a one type of affair where information is provided by a company and saying we have sufficient knowledge, the reviewer has to agree or not agree that it is sufficient, and this poses a new burden on the review division. And I don't know how we can cope with that because we haven't been able to cope, apparently, with the differences that already exist.

DR. HUSSAIN: That is a very good point, and I think that's the challenge that we do not underestimate. We actually recognize that quite well. Let me share the background.

As we started the PAT process, this was one of the challenges, and quite early in the process we decided that we will have a team approach to this and the team will be trained and certified. So the PAT-based submissions that will come in will not got to any person randomly or the way we assign it. It only goes to the team which is trained and certified.

Now, we had the luxury at least from the perspective we anticipated submissions coming, so we had

time to train ourselves and the team and be ready for that. In fact, we have to hurry up now because the submissions are coming faster than we anticipated. But we'll be ready for that. But that's a small sector.

Now, if this is successful, we have two options. One is to ramp up and train the rest of the staff quickly to be ready for that. At the same time, we have strategically hired some other individuals with the right expertise to be part of this team. Training/certification only takes you to a certain level. Having the right experience, having the right technical know-how from the start is also critical. So we have a strategic hiring program where we're actually aiming for chemical engineers. We're aiming for industrial pharmacy types. So that's sort of a two-pronged attack to that.

Now as we move forward in this initiative, you will see a transition whereby we have already announced a quality system approach to the review process. Now, science- and risk-based approaches to review have to come in. In a quality system approach, one of the components could be a scientific peer-review process. So that's brings in a level of consistency.

So I think we are looking at a different number of mechanisms to bring not only the scientific level up through training, hiring the right people, quality systems

for review, and actually move towards a continuous learning concept within the system. But we're doing that not by saying we have to change the system. This system is functioning. We have created a new system for PAT. It's a small one and we'll learn from that and move into a continuous improvement model without disrupting the current system. That's an evolutionary process.

DR. GOLD: Ajaz, I hear you and it sounds great. I think we better be certain we have dispute resolution in place before we try it.

(Laughter.)

DR. BOEHLERT: We're winding down as far as our time. Are there last comments from members of the committee? This is your opportunity.

DR. RAJU: Since the word manufacturing science and process understanding has come up so many times -- and there is an absolute nature to it -- I think it makes sense to have a general putting on paper of some of its components and then a more specific set of specific circumstances in which it applies that might be similar to SUPAC. SUPAC is more of a level 1 or level 2 kind of a situation, but I think we have to have a framework piece done. Otherwise, we'll have another level 2-and-a-half piece, and we're going to all fight one by one with data and information.

So I think it makes sense to have an overall framework piece around what is process understanding, its dimensions, its characteristics, and how might you measure it. And then with that kind of backbone structure, we can have individual pieces based on equipment or technology and changes that has a regulatory context to it.

Now, the question then is, if that's the case, who should write it? And it should be broad enough and it should be general enough and it should be objective enough and neutral enough. I think it would make sense that there would be that general framework and then the specific pieces, like a hub and spoke or something like that. That's my thought based on what I heard today.

DR. BOEHLERT: Others? Going, going, gone. This is your last chance. I think it's the end of the day and folks are ready to call it a day.

Ajaz, any last comments?

DR. HUSSAIN: No.

DR. BOEHLERT: If not, we will close the meeting. Meeting is adjourned. Thank you all.

(Whereupon, at 4:22 p.m., the subcommittee was recessed, to reconvene at 8:30 a.m., Thursday, May 22, 2003.)