DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PROCESS ANALYTICAL TECHNOLOGIES SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Tuesday, February 26, 2002

8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Thomas Layloff, Ph.D., Acting Chairperson
Kathleen Reedy, Executive Secretary

MEMBERS

Gloria L. Anderson, Ph.D.
Joseph Bloom, Ph.D.
Judy P. Boehlert, Ph.D.
Arthur H. Kibbe, Ph.D.

SGE CONSULTANT

Melvin V. Koch, Ph.D.

GOVERNMENT PARTICIPANT

William F. Koch, Ph.D.

OTHER GUESTS/SPEAKERS PARTICIPANTS

Thomas J. Hale
Leon Lachman, Ph.D.
Kenneth R. Morris, Ph.D.
G.K. Raju, Ph.D.
Eva M. Sevick-Muraca, Ph.D.

INDUSTRY GUESTS/PARTICIPANTS

Robert S. Chisholm
Rick E. Cooley
Doug Dean, Ph.D.
Steve Hammond
John C. James, Ph.D.
Ronald W. Miller, Ph.D.
David Richard Rudd, Ph.D.
John G. Shabushnig, Ph.D.
Leon Shargel, Ph.D., R.Ph.
Efraim Shek, Ph.D.
Jozef H.M.T. Timmermans, Ph.D.
Judy Wong, M.S.
Jerome (Jerry) Workman, Jr.

FDA

Yuan-yuan Chiu, Ph.D. (Sessions I, II, IV)
Douglas I. Ellsworth (Sessions I, III)
Joseph Famulare (Sessions II, III)
Ajaz S. Hussain, Ph.D. (Sessions I, II,IV)
Moheb M. Nasr, Ph.D. (Session III)
Michael C. Olson (Session IV)

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LAYLOFF: I would like to call the meeting to order, and we will start with Kathleen.

Conflict of Interest Statement

MS. REEDY: Acknowledgment related to general matters waivers for the Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science, February 26, 2002: The Food and Drug Administration has prepared general matters waivers for the following special government employees, Drs. Judy Boehlert, Gloria Anderson, Joseph Bloom, Thomas Layloff, Robert Lodder, Melvin Koch, and Arthur Kibbe which permit their participation in today's meeting of the Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science. The subcommittee will discuss strategies to explore issues in the following four focus areas: a) product and process development; b) process and analytical validation; c) chemometrics; and d) process analytical technology, application and benefits, being held by the Center for Drug Evaluation and Research.

Unlike issues before a committee in which

a particular product is discussed, issues of broader applicability, such as the topic of today's meeting, involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact on so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member. 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.

We would also like to note for the record that Leon Shargel, of Eon Labs Manufacturing, and Efraim Sheik, of Abbott Laboratories, are participating in this meeting as industry representatives, acting on behalf of regulated industry. As such, they have not been screened for any conflicts of interest.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments. We would like

to disclose that Dr. Leon Lachman is the president of Lachman Consultants Services, Inc., a firm which provides consulting services to pharmaceutical and allied industries. Dr. Kenneth Morris would like to disclose that his department receives funding from pharmaceutical companies directly or in consortia programs. Dr. Gokaraju Raju would like to disclose that he has contracts and grants from Pfizer and the Consortium for the Advancement of Manufacturing of Pharmaceuticals. Dr. Raju also serves as a consultant and speaker for these firms. In addition, Dr. Raju is employed by and has a fiduciary relationship with Light Pharma Inc. Finally, Dr. Raju has affiliations with MIT and Purdue University.

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 are aware of the need to exclude themselves from such 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 with to comment upon.

DR. LAYLOFF: Thank you.

I have a few remarks I want to make. First of all, Ajaz has pulled together the most knowledgeable people he could find to work on these topics. For all of us it is a great opportunity and a great responsibility for us to advance the application of good science to process control and the application of good science to regulation, which we frequently hear.

[Slide]

Our focus has always been on the active pharmaceutical ingredients, from alpha to omega. Alpha is the incoming active pharmaceutical ingredient and the technology change that came with chromatography brought a revelation to us about impurities. In the other technologies we also focus on the active pharmaceutical ingredient. Omega is the bioresponse or bioavailability. That became known to us primarily through the RIA studies on digoxin in the '70's where the drug was probably killing several thousand people a year.

[Slide]

So we focused on the alpha and the omega, and that big middle part is where the process is.

Some people may disagree with me, but we have treated the API as the process surrogate marker. It is a univariate handle on a polyvariate process. That focus has had little regard for excipients and the process itself in the past. We have shown in many instances that it is actually a poor surrogate for many components in the process through failures at the omega stage.

[Slide]

The tools -- the assessment tools and technologies are available; the data support systems are available to improve product consistency, reduce bad products and reduce recalls.

[Slide]

Our job, should we agree to accept it, is to help guide the guidance development to bring it together. The FDA is waiting for our help and assistance. Will we be able to answer the call?

[Slide]

Keep it general. Leave for another venue and time assessment technology details on calibration, repeatability, reproducibility and so forth. Focus on the questions posed in the handout. Raju has his pen poised ready to draft.

Chris is ready to manage the process. The ball is in our court. Now I would like to call on Ajaz.

Introduction, Overview and Objectives of the Subcommittee

DR. HUSSAIN: Thanks, Tom. Some thoughts before you break out into the four working groups. As Yuan Yuan yesterday mentioned, I want to reiterate that the guidance that we are planning is not a how-to guidance; it is a general regulatory process guidance. For that, the information we seek is to be in terms of what are the acceptance criteria for a new technology to come in; not how you would develop that technology or how you would bring that process through. The focus is on a regulatory process rather than how do you calibrate or things of that sort. So, keep that in your mind as you sort of break out.

If you could focus attention on the questions that we have asked and help us, at least at the end of this meeting, to identify the key topics that need to be in the guidance, essentially create an outline for the guidance that we are planning to develop. I have provided you an outline that we have right now. When we come back to meet with you for the second meeting, we hope to

have at least a draft in our minds of what the issues to be addressed in the guidance will be and how we plan to address that. So the next meeting will be very much focused on very specific questions that we will bring to you at that time. So, for today keep the focus on the general principles, as well as what needs to be covered. That is about it. Thanks.

DR. LAYLOFF: Thank you. We will be breaking into our working groups shortly. The target for each work group is a fifteen-minute presentation this afternoon, which will be timed, followed by a fifteen-minute timed discussion.

For those of you who are agenda watchers, we had no one ask for a public hearing or statement at a public hearing. So, we will take that time and fold it into our program time. Our morning sessions will run from 8:30 to 12:30. We will reconvene at 1:30 for presentations and, hopefully, pick up half an hour on the agenda. Again, a fifteen-minute presentation is the target, and I will turn it over now to Kathleen.

MS. REEDY: A couple of details, the name of the working group and the list of people who are attending that group are on the door of each of

these rooms, and the questions are on the table, once you are in there. The questions are also in your folder.

In this room, which is the Walker-Whetson room, is the process and analytical validation working group. Leon Lachman is the facilitator, acting chair, Thomas Hale, Jozef Timmermans, Robert Chisholm, Kennedy Chibwe, Carl Anderson, John James, Sonja Sekulic and the FDA liaison and support are Doug Ellsworth, Moheb Nasr, David Morley and Lucinda Buhse.

In the very next room, the Goshen room -- you need to go out and back in the next door, is the process analytical technologies, applications and benefits working group, chaired, facilitated by Arthur Kibbe, William Koch, Eva Sevick-Muraca, G.K. Raju, Steve Hammond, Kenneth Leiper, David Reed, Doug Dean, Claudia Okeke, Russell Madsen, Silvano Lonardi, and the FDA liaisons, Tom Layloff, Chris Cole and Peggy Cunningham.

Chemometrics group, Potomac room. As you leave this room, go down to your left, right where the restrooms are, to the next corridor and to the left. The Potomac room is also the second door on the left. Melvin Koch, acting chair, Robert

Lodder, Rick Cooley, Jerry Workman, Brian Curtiss, Dwight Walker, Andrew Lange, Edgar Neil Lewis, Svante Wold, and the FDA liaison, Ajaz Hussain, Marilyn Welshenbach, Jonathon Cook, Jack Spenser and Everett Jefferson.

Washington room, also past the restrooms, to the left but the second door on the right, product and process development working group, chaired by Judy Boehlert, Kenneth Morris, Ronald Miller, Dave Rudd, Judy Wong, John Shabushnig, Walter Dziki, Thomas Cambron, Gopi Vudathala, Richard Remmele, Anserd Fraser, and the FDA, Yuan Yuan Chiu, Frank Holcomb, Kathy Taylor, Ron Lyon, Lawrence Yu.

DR. LAYLOFF: Thanks very much, Kathleen. We will adjourn now to our working groups. Break your session at 12:30. Have your presentation completed before you break. At 1:30 we reconvene in here for reports from the working groups. Thank you.

DR. HUSSAIN: Just to clarify, all our open meetings so people from the audience can attend those meetings.

DR. LAYLOFF: Yes, this is an entirely open meeting so feel free to attend whichever

session you wish.

[Whereupon, the proceedings were recessed at 8:15 a.m., to convene in working group discussions, to be resumed at 1:30 p.m.]

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A F T E R N O O N P R O C E E D I N G S

DR. LAYLOFF: Thank you. Our first presentation will be by Dr. Kibbe, on applications and benefits.

PAT Applications and Benefits

DR. KIBBE: Greetings. First, I want to thank the committee for their efforts, the working group. I have always aspired to be in a meeting populated by brilliant people working towards a common goal without rancor and disagreement, and I have had the privilege today and I really appreciated that.

One of the difficulties of being vertically challenged is you have to move the microphone. I always tell people I am not overweight, I am under-height. If I was the height I wanted to be, I would be the ideal weight.

What we did during the morning is we examined the issues that were given to us. We have a few slides which I hope I will be able to get started here.

[Slide]

We started out as we first looked at the definition of PAT, and our discussion revolved around some of the word-smithing, and we have made

a small change in the definition that was originally presented to us. One of the concerns we had is that people not think narrowly of the word "analytical," that analysis and analytical applies to more than just what we normally deal with in terms of chemical analysis.

[Slide]

So even though we left the word "analysis" in there, we did a little bit of word-smithing with it. First, we took out the term "continuous" and we added the word "critical" because we were concerned, in some parlance, that there would be a lot of information gathered and not all of it be critical and, therefore, even though we are gathering tons and tone of information we wanted the process, as it is defined within guidances, to reflect more the critical parameters than every single parameter we could pick up.

We then looked at the list of questions and we used them as a stimulus for discussion. We didn't specifically respond to each question, although we discussed each question. We used them as a way of carrying on a discussion of PAT and the applications of it to the industry and the benefits to the industry. We generally agreed that PAT

could be applied to any process and that it would have a benefit if applied correctly. And, it would have a benefit if we did not limit it to any specific tool but expected that multiple tools would be used and new tools would be invented. At the rate of the evolution of technology nowadays, new tools come to us at a moment's notice.

Barriers, we thought, really revolved around cost and money. If there was a perceived loss of revenue because the process slowed the introduction of a drug to the marketplace, then the companies would not be as prone to go along with developing PAT. If there was a perceived negative impact of regulatory oversight, then they wouldn't go along with it. Both of these really broke down to how much would it cost a company to do it; what it would cost a company in potential risk in terms of dollars, and so on.

[Slide]

Then we got to the real meat of the matter, as you will, and we discussed question eight, which is what has to be in the guidance to give it the kinds of impacts that we want? What we were hoping for is a guidance that really established an environment in which industry was

not only allowed to come forward with PATs, but was actively encouraged to bring them forward in a non-punitive environment where the development of these process control systems would not have a large negative downside.

First we said that the guidance must allow the development of a PAT whose endpoint is a signature of the quality of the process and the process is well understand. We didn't want to use models because models have certain kinds of implications to them as a terminology. We didn't want to use fingerprints because we have used fingerprints in other kinds of analytical tools. So, we used signature. We are not married to that term but we certainly don't want to put a term up there that isn't specific for this process and would make people think in very specific terms about other processes that they might be involved with.

The guidance implies that PATs would be used in an environment of continuous improvement without regulatory burdens that would inhibit that. We are concerned that we see PAT as a way of constantly improving the quality of everything we make and do, and if the regulatory environment is

such that it would cause the company to put together a particular process and then have to live it for 15 or 20 years we wouldn't be getting there. So, somehow the guidance has to stimulate the industry to go ahead and use PATs and constantly improve on them, and use that information to improve on their process and, therefore, improve on their product without concern for an extra burden to be added to the process because of it.

[Slide]

All products have critical quality attributes. We agree that that was true. We say that process variables exist that can be controlled to maintain the critical quality attributes within acceptable limits. We agree then that PATs are applied to achieve both understanding and control of process variables and that our causally linked to product critical quality attributes. We think this is an extremely important set of concepts that need to be incorporated in the guidance so that people know where we are trying to go.

[Slide]

There are new and developing measurement tools and guidances should not limit the selection of a tool for a PAT. The guidance should be very

clear that it is not a guidance for a specific tool or a specific process. We argued -- not argued, we discussed because we were brilliant people discussing brilliant ideas the possibility of including examples in the guidance of successful applications of PAT, and we reasoned that to include them would be to bias people in the direction of that tool or application and not leave it open. We would prefer the guidance set rules for general acceptability of those things without undue pressure by giving an example which was acceptable. We know that in the regulatory environment companies often will exactly mimic somebody else's successful application just for the purposes of making sure they will make it.

We want to encourage companies to move away from the current univariant prescriptive testing to multivariant focused measurements. We use measurements specifically to get away from the implications of analysis.

[Slide]

"Encourage" is underlined on purpose. We feel, or felt, or agreed that to allow companies to do it really isn't getting to the spirit of where we want to go. PATs seem to us to be a beneficial

methodology. That beneficial methodology not only benefits the company and, therefore, should be viewed by them as an economic incentive to put in place, but it benefits society in general and the quality of the products that we have.

With that in mind, we should recognize that as companies go in this direction, it becomes the norm. It will automatically become part of CGMP and, hence, the agency will eventually get to the point where it is requiring it or looking for it. This brought us to a very interesting discussion, something that we need to include in the discussion and planning for the guidance but not necessarily in the guidance, and that is that if the field people and the review people both don't agree on what is going on, and what a PAT it is, and how to review it, and how to evaluate it, and how to look at it this whole thing will fall apart before it gets off the ground.

So, part of what has to happen from the FDA perspective and from industry's perspective is that field and in-house reviewers have to all be on the same page. If the guidance is going to work and if we are going to feel encouraged enough to submit processes that we have developed through the

agency, the agency has to be prepared to accept those at both the review level in the Parklawn Building and out in the field in the middle of Denver, or wherever they are going to.

[Slide]

We think that PAT can apply to all six of the manufacturing sub-processes which includes inbound logistics, active ingredient manufacture, bulk formulations, fill and finish, packaging and outbound logistics. One of the areas that we talked a lot about was the quality excipients, variability among excipients, how that variability is translated into variability and quality, whether that variability is an acceptable level or an unacceptable level, and what-have-you.

Stability testing should be considered as part of this process, or at least an additional sub-process. So, we didn't think that PATs should be limited to any one aspect of what is going on. If someone has PAT they can put in place that will take care of inbound logistics, we should encourage them to do so.

[Slide]

The guidance should recognize that new insight into the process, which does not affect the

quality of the product for its intended use, should not require mandated changes in the process. One of the fears I think that we all have is if we go looking real hard at new ways of looking at what we do, we will find problems that we didn't know exist and what level of change will be mandated from that? One of the things that we want the guidance to be able to say is that if the variable that you discovered, because you have been able to characterize your process much more clearly than you had in the past, is something that will help you in terms of your in-process procedures and save the company money, fine; go ahead and do it. But as long as it isn't adversely affecting the product outcome, the usability of the product you make, the health benefits of the product you make to the consumer, then we, as an agency, will not mandate. I think it is important that that be in there to give the companies a little flexibility in how they respond to what will be an ocean of new information.

We would like the agency to recognize that PATs have a potential for replacing a lot of classical or current methodology in terms of quality control routine testing methodologies, and

the guidance should recognize that PATs will, in large measure, replace current validation requirements for process validation. Because PAT goes to the issue of on-line constant validation every time you run the process, why have another set of validations that don't really get to the issue when this might very well solve that issue for you?

The guidance has to define what records have to be kept and for how long. A sea of data will be generated. Thousands and thousands of data points on a very simple in-process measurement tool could be generated. How long do you have to keep it? How much of it do you have to keep? Is it going to be an electronic storage nightmare? I think the agency has to look seriously at how long does in-process data, generated from a system which is intended for both measurement and control of the process, need to be kept, and which pieces of data, which critical pieces?

Then, how do you involve FDA in the PAT development and implementation? One of the things that we talked about and we encourage is the agency establishing a contact place for companies to go to begin the development and implementation of a PAT

process at their site. Now, we recognize that companies will be playing with this stuff, getting it on-line and feeling comfortable with it before they go to the agency because they are not going to go there with something that will never work. But, at the same time, how do they go there efficiently? Is there some office, some ombudsman who is going to be favorably disposed to help them to make the transition from classic measurements and classic quality control/quality assurance measurements to a PAT that will supplant some of those things?

That is pretty much where we got to. I guess we are in line for questions. I encourage the brilliant members of my committee to respond to questions since I clearly was there just to make sure that we all had enough coffee and orange juice, and the rest of you did all the heavy thinking. Tom?

Subcommittee Questions and Answers

DR. LAYLOFF: It is open for discussion. Any questions for Dr. Kibbe?

MR. COOLEY: One question I have, I was wondering why your committee chose to include control as part of process analytical technology.

DR. RAJU: We actually talked about PAT

and said that maybe PAT should stand for process assessment technology in some ways, and just measurement wouldn't be enough and we had to find a way to connect the loop back to process understanding. Along with that, we began to define what is analytical. Does that simply mean a chemical measurement or is it a process of thinking and analysis? So, we would like to find a way to put the next steps into the thought process in terms of capturing the benefits, without being limited primarily to the measurement, although we know the measurement is the way to get there.

So, we tried to be a little bit inclusive in that sense. And, there is no clear yes or no in there. In a couple of places we tried not to give examples because we didn't want to limit the thinking. If you notice, in a couple of places we said the risk has to be managed. Number seven is probably one of the important points in terms of managing the risk of what we see. You can choose whether to include control or not, and this was our thought process around it.

MR. COOLEY: Just another comment, the automation community has obviously progressed way ahead of the measurement community as far as at

least on-line measurements. I am just wondering what the benefit would be in trying to encroach on what is already an established standard, more or less. In most cases the analytical measurement is going to be a totally independent system that provides an output to a DCS or a control system. There may be some cases where that is not the case but probably 99 percent of them will be ones where we are just providing an output.

DR. RAJU: I think our focus was on controlling in the abstract sense in terms of the processes. We did focus mostly on the measurements but since the connection back to process understanding had kind of the abstract level of product and process control, I think that was not our thought process.

DR. KIBBE: I think it is difficult to put in place a system that measures how well something is going on without it somehow feeding back into continual quality improvement on that system. In that sense, you have analysis and control linked. It is not that we thought this would be necessarily a replacement of your quality control lab -- necessarily.

DR. SEVICK-MURACA: May I make a comment?

I was on the committee and I guess I didn't think of Rick's point. He makes a very good point in that if you do classical control, the statement "control" means that you are leaving the control of the process up to that measurement itself and that requires change in the process. So, I don't think that was the intention that we had. I think, if I am correct, that is where you are coming from. We might want to consider getting rid of that "control" because if someone at the FDA or somebody else is looking at it from the classical standpoint of that word, Rick is entirely correct in his assessment.

DR. MILLER: Could you explain the rationale behind the underlining of the word "encourage" and the other comments that you were saying?

DR. KIBBE: We accept the premise that the application of PAT is a benefit and it could be, depending on the methodology and the tools, applicable to every dosage form. If that is the case, then why simply allow, why not encourage? I think if the companies come to the realization that there is a benefit gradually the number of companies that have these processes in place will

go up, and that will become the standard in the industry, which is CGMP, and will eventually become encouraged because it is naturally the standard for quality in the industry. So, why not recognize now that we are really talking about encouraging the industry to move forward with a system that we, at least as an advisory committee, think is going to be valuable for the industry and the public?

DR. RAJU: The other thing was to consider the possibility that FDA not only be a policing agent, but I think to help in the education across because we both win together. It is kind of a new role. Simply saying it is allowed, I think is already in place but just allowing doesn't seem to be working and maybe we have to have a framework in which we can find a way to both win. So, we are encouraging so we can both be encouraged together. I don't know if this will be enough but I think it is one step.

MR. COOLEY: One comment on the retention of records, would not this kind of data fall under CFR 21, Part 11 already, which is already a guidance for electronic record retention? Is it really necessary to produce a separate guide that actually may end up conflicting with one another?

DR. KIBBE: True.

DR. RAJU: I think the recording was also an issue of what information should we gather; how long we should keep it; what are we accountable for. So, the CFR Part 11 and the signature and the consistency is, I think, in place for a long time but the other aspects --

MR. FAMULARE: I am sorry, not only the Part 11 but the GMPs themselves, you know, have time frames for record retention at which time, for example, two years after or one year after the expiration date there is no need to keep the records anymore. So, I think that there aren't limitations that exist in the current framework so unless an argument is made that the system will outstrip what is already in current regulations, I don't think we need to go there in this guidance.

DR. MORRIS: But maybe it is enough just to say that the criteria will be the same as covered in the current guidances, just so it is clear in this guidance that it is not a different thing.

DR. LAYLOFF: One example that was given to us was a videotape of a mixing process that they were running over and over again. So, each time

they ran a mixing they ran a videotape. The question is, is the videotape and electronic record that you have to keep? Each time you run the storing action you run a videotape. Does that become a permanent record then that you keep under Part 11? Or, is it something that you dump when you get done and you release the product?

DR. KIBBE: I think there is sufficient opportunity for unknowns that it is worthwhile at least for the agency to recognize in the guidance that there might be a concern for the quantity and quality of the information that is retained.

DR. LAYLOFF: I think the amount of information that could be generated by this is actually astounding. I think retention for one year or two years after expiration is not unreasonable for the release issue, but if you are talking about end-process controls where you are generating maybe sensors at 20 different sites continuously there is a huge amount of data. There might be something that should be considered at some point by the agency as having an alternate procedure to deal with it, set some specification. Otherwise, under 21, 11 you are going to need huge amount of storage and it is not useful.

MR. FAMULARE: I think these issues have already arisen in terms of Part 11, and I don't think we want to take on Part 11 as part of this guidance in those issues. Those issues preexisted the advent or the encouragement of this technology and the agency already recognizes that there are issues surrounding Part 11, and there is a whole working group working on that. Maybe the best thing to do would be to feed this as a factor in that working group, led by ORS's office in enforcement.

DR. LAYLOFF: It is just an issue that should be brought to their attention.

DR. RUDD: This might sound quite patronizing but I just wanted to congratulate the group on the output. I am very nervous about the output from these four groups because it is very critical, but from the GSK perspective you have captured the concepts and the principles beautifully. I am delighted to see what you have come up with. It is also as if I could have been there myself. Thanks very much.

DR. LAYLOFF: Are there any questions from the rest of the working groups? If not, we will now move to Judy Boehlert, product and process

develop.

Product and Process Development

DR. BOEHLERT: All I can say to Art Kibbe is that I am as tall as I want to be, so I don't know what my excuse is.

I would also like to thank my group. I think we had a very productive working session. Everybody contributed and that was very good. We had some lively discussion and, in fact, we were able to get done a little bit ahead of schedule so we addressed an added topic and if I have time, I will go over that as well.

[Slide]

We did go down through the questions but some of them turned out to be redundant. In fact, when we looked at the list we decided that question number one we would hold till last. So, when you see our answers to question number one, they are fairly brief because we addressed everything in question one by looking at the others that were there.

This one has to do with what considerations during product development might you consider. This is brief because we are going to address the basic issues in later statements.

Everybody agreed that the benefits of PAT are under-realized, under-utilized. People don't know they are available. Some companies have tried it and perhaps haven't see the benefits they have expected, and that has led also to sort of reticence to do more. Until you know that there is a real benefit you don'[t want to expend the energies.

[Slide]

There is still some selling that needs to be done. Clearly, everybody is not on this bandwagon yet. And, 6 sigma as a target is really too high. What was suggested by the members of our group was maybe somewhere in the range of 3-4 as a more reasonable target.

[Slide]

We talked about what areas you might want to apply PAT technologies to, and it is applicable to most areas of the manufacturing process but there are different levels of maturity for the analytical technologies that are used. It is probably most mature when you talk about the raw material; less mature when you talk about blend samples; and perhaps even less mature when you start talking about final product. So, yes, it can

be used in all of those areas but the degree of maturity for the techniques is not the same. The nature of the ingredient is also a factor. It may not work in all cases. Where it works, it may work very well. In some cases it doesn't.

[Slide]

The most important thing about PAT technologies is that it allows incorporation of feedback controls, such that you can adjust the batches you are processing and you may not need to lose a whole batch. During development is when you are going to start taking a look at PAT. The goal there is to understand the process and develop one that is very robust.

Also during development, and this is a key point we wanted to make, is that you may look at a lot of different parameters using PAT techniques, but what you don't want to do is look at all of those parameters once you go to market. The goal during development is to identify those that are important and those that are needed, and then select those that you wish to monitor during product that most critically control your process. It is sort of like doing stability studies and identifying impurities and degradants. You find a

lot of things during development. You do stress testing. But during actual product what you test is limited. Evaluation from other technologies from other industries may also be helpful for people deciding what it is they want to do, and how they want to do it.

[Slide]

Unit technologies where you have a history and possible technologies that may be used can occur in the guideline but they shouldn't preclude the use of alternative technologies and methodologies. We never want to limit the ability of somebody to use something new. You know, there are some well defined examples out there now, but technology keeps advancing and changing.

This one had to do with how you anticipate application will change the process for identifying critical process variables -- definitely a development function, a structured approach, getting to know your process early, optimizing it, identifying critical parameters and developing the metrics. How you control it is going to be up to you. You are going to decide that. On-line sensors give you additional information certainly to control critical endpoints.

[Slide]

As was mentioned by the previous speaker, certainly moving from univariant to multivariant approach in strategies may be identifying parameters that are important to the process that we didn't look at in the past. We need to be able to correlate PAT with specifications where that is relevant, and there is a lot of work left to do in this area. Looking at the quality of the raw material, of course, is basic to everything we do. You need to control the inputs to the process at the very beginning.

[Slide]

We talked about what are some of the issues that arise during scale-up. Do PATs help in the scale-up situations? The answer is yes, of course, they do. If you know more about your process, it is always going to be a help. You need to know what endpoints you are working towards. You need to know what the process should look like when it is working well.

We also talked about a process signature. It was a term that came up in our discussion. When it is working well and you get to know what that is. When you scale-up, of course, it may change.

Scale-ups sometimes don't do what you think they are going to do but by doing the PATs early in development you know what things are important to monitor, and then you can identify those changes.

[Slide]

All of these were questions. Do they cause problems? Yes. I mean, we could make very simple answers to everything. One of the limitations we saw is that some of the off-line testing methods we use as gold standards may not, indeed, be as good as we think they are in showing us product quality, and the example we used was dissolution.

There are engineering issues that need to be looked at -- critical implantation issues, applying design of experiments, business issues and this came up in the other meeting. Addition of a PAT to a process must be value added. For new product sensor applications up-front equipment is easier to put in place and employ. Most people felt that the easiest place to use PAT is with new products. Yes, they can be retrofitted to old products but it is not quite as straightforward.

PAT measurements may not match your submission parameters even though your product may

still meet your submission requirements. This is an issue that came up yesterday, and one that needs to be made clear.

[Slide]

Moving from parameter controls, which is what we are talking about, endpoint control is a desirable outcome. However, we did discuss that even with parameter control you might need to set boundaries, either upper or lower limits; it is not anything goes. Low dose drugs, of course, and low potency may be exceptions and PAT technologies may not be as applicable. Do they make scale-up transitions easier and, if so, why? Yes, of course, because you better understand your process.

[Slide]

In some situations PATs may be used only for certain specific operations within the overall scheme of dosage form manufacturing. And, this was either what are advantage or disadvantages to applying PAT to only a specific unit operation. We didn't see any technical downside to doing that. It is a business decision. Whenever you are applying PAT, it should be value added. Accurately reflecting what is going on in a process can't really be a disadvantage.

The overall weakness comes when you do that. For example, if you have blend homogeneity and you are looking at the blend, downstream you could have problems and if you are not looking at anything downstream perhaps you wouldn't identify it. So, you need to be careful. If you are only applying it to one unit operation you need to make sure you understand the rest of your process.

[Slide]

When you to for new technologies, of course, you have to pay for the technologies and that is where the business aspect comes in. There are time considerations. There are human resource considerations. They all have to be taken into account. One advantage we saw for applying PAT to unit operations is if you were to develop it, for example, for a dryer for one product. Then, the applicability to other problems that are dried in that same dryer should be there; should have to do a lot less work to bring it into place for those other products.

[Slide]

Can PATs be used to prevent out of specification incidents? Well, certainly, implementing PAT on a poor process is not going to

change the number of OOS results. But if you are allowed to go to an endpoint in your process, you may be able to control the process in such a say that you do, indeed, eliminate those OOS events. It will decrease these incidents and make the process more rugged. Also, if you have PATs incorporated into your process you will have a much better chance of doing a much more rigorous scientific investigation when things go wrong.

[Slide]

Can PATs be tools for predicting performance of a drug product, for example, dissolution? The answer was it is certainly possible. What we need to do is develop the correlations that are necessary to do that. They are not all there right now. It is an exercise, as always, in benefit-risk assessment and much more work needs to be done. We heard the other day about the use of the acoustic technologies. These are things that can be used. They are just not mature technologies at this point. Also, it is probably going to be on a case by case basis.

[Slide]

Can they be used for predicting the stability of a drug product? If yes, what are the

factors? Well, what we said is that the use of PATs in a process will not replace stability testing. It may be used as a predictor however, particular for things like physical instabilities. If, indeed, you have more knowledge of your process, then you have more confidence that your product is going to remain the same throughout its shelf life. It may reduce your risk, for sure, and may be able to predict better what your stability will look like.

[Slide]

One benefit for batch release will be higher quality. Product failing during shelf life will be less likely, and that is fewer recalls. More consistent product is always a better option.

[Slide]

Finally, we looked at what factors the industry and the agency should consider while implementing use of new PATs for already approved drug products. We need to look at the benefits of that. In a new product it is easy. You can build the quality in. It is not the same on an old product. Consistent monitoring of an ongoing process is always a good idea because you yield better information on your product and

considerably, as we said before, much more opportunities for new products.

[Slide]

It could have applications to validation and SUPAC guidelines in the future, and we think this is definitely something that should be considered. If there are no problems with your current process, we did not see a sound reason to make changes. Unit operations validated for one product, and we said this earlier, may be used for other products and we would like to see those incorporated through SUPAC.

[Slide]

The view from industry in general is if it's not broken let's not fix it. There needs to be a persuasive reason to make changes. If you make changes, like a vendor change or a site change, it may be a very good opportunity to look at your process and look at the need to incorporate PAT. the goal of having team inspections we see as a positive kind of benefit because our concern is the same as the previous group's. You have the review chemist and you have the investigator and they may not be looking at these technologies in the same manner.

[Slide]

That was sort of the agenda that was laid out for us and the issues that we needed to look at. We took a look at the table of contents to see if what was anticipated to be included in that table of contents correlated with what we had in mind. I won't go through some of them because, you know, you can combine this section with others.

We did ask that the FDA consider use of PATs in product development and some description of what that entails, enabling technologies including chemometrics -- some discussion of that. The relationship of PATs to finished products specification. We felt that it would be important to have worked examples of different dosage forms, if not in the guidance then by reference.

[Slide]

Guidance also should address the roles and responsibilities of different groups. Manufacturing, product development are obvious, but also the quality unit, engineering, process technology as well as others, as well as the skill mixes that we might need in the future because the skills that you are going to need from your employees are going to change as we move into these

new technologies.

With that, thank you for your attention. I will ask my committee members also to chime in if they have any comments and we would be happy to address your questions.

Subcommittee Questions and Answers

DR. LAYLOFF: Any questions for Judy?

MR. COOLEY: Judy, could you comment -- if I wrote it down correctly, you said that a technique validated for one product and unit would be okay to use for another product?

DR. BOEHLERT: The operative word I think is "may be." You know, we are looking at things like drying where the principle behind that technique is pretty consistent product to product and what you are measuring is pretty consistent product to product. You may be able to do that database generated for one product to perhaps not do so much work on a second product; that you use that same piece of equipment and technology for it. Do I make myself clear?

MR. COOLEY: I think so. I just want to clarify that you are not saying that you do one validation package for a NIR-IR in a dryer, for example, for product A and then, when you bring in

product B, you don't need to repeat your validation.

DR. BOEHLERT: Absolutely not. We were looking at techniques such as drying where, you know, you might not have to do as much work on the second product as you did on the first.

DR. RAJU: Judy, how did you conclude that we couldn't reach 6 sigma and we could only do 3 to 4?

DR. BOEHLERT: We had a statistician in our mix.

[Laughter]

DR. LAYLOFF: Members of the working group can ask questions also, if you like.

DR. BOEHLERT: Or make comments.

DR. HUSSAIN: I think one of the challenges, the reason we wanted to have some discussion on this is that at some point my though process was that you really have to do it at the development stage to get the full benefit. To do that, you have to think of setting specifications differently than you are used to, going from time to a performance-based specification. So, that needs to occur early. Then, the scale-up has to be built around that. So, we are shifting the

paradigm in terms of how we are setting specifications. I didn't get much on that part of the discussion, if somebody could add to that.

DR. MILLER: Ajaz, we didn't touch on the specifications. That wasn't one of the charter questions. We felt the chemometric group was going to provide some insight.

[Laughter]

DR. HUSSAIN: That was one of the first questions we posed to you. Chemometrics will not answer the specification question, it is more on the modeling and what sort of criteria we judge those models by. Specifications will have to be product oriented.

DR. MILLER: Well, we did speak to what we needed to focus in on the critical aspects and that, on first blush, may be a wide number but we made it very clear that we needed to narrow it down to the specific aspects, specific critical points that control the process and that is what we wanted to go after. Now, to the degree of certainty, we didn't quite get into that aspect.

DR. HUSSAIN: But if I phrase it this way, that your group would be in agreement with the concept of going to performance-based

specifications?

DR. MILLER: Totally.

DR. LAYLOFF: I think that is a universal sense around the table, that process validation like timing and things like that are not appropriate when you can have sensors to move to performance basis.

DR. MILLER: And, therefore, there wasn't so much debate about that. We were taking other tracks.

DR. SHABUSHNIG: I think also it is a little bit of a chicken and the egg situation in the sense that right now we are developing the measurement technology and learning what those measurements tell us. Based on that, you can then set good specifications. I don't think we are at the point today where we can determine those specifications a prior and then work our way back. So, I agree. I think we are all certainly in support of that concept as you are describing it but in terms of where we are, from a technological standpoint, I think we are moving to that by getting the measurement technology in place and deciding what new information we can glean from the new measurement technology, and then use that in

the specification setting process.

DR. LAYLOFF: If you said something like blend to consistency, what does it mean? No change over ten seconds or thirty seconds? What does the specification mean?

DR. HUSSAIN: This is more for Steve Hammond, if I recall correctly, yesterday he mentioned that one of his new assignments is setting up PAT stability testing. My personal sense is that I don't think this technology will give you more information on stability. If you can share some thoughts on that?

MR. HAMMOND: Well, there are technologies out there that are super sensitive particularly to the degradation of APIs. I would guess the way we are thinking is focused on the API, although that may not necessarily be correct. But you can use various techniques to look at the surface of tablets or even, indeed, to look at the blend binding stability, techniques like fluorescence and some of the mass spec methods that are there. There are technologies that are very, very sensitive. In fact, some of the indications we have had are that they are actually more sensitive than the traditional methods, which could be a real

issue.

DR. LAYLOFF: I think also that focusing on the API probably is not a very good thing to do in the long run because of things like the physical relaxation of the solid dosage forms that might change the dissolution characteristics also. Polymorphic transitions could occur.

MR. HAMMOND: The thing about focusing on PAT measurements, usually one of the main focuses is that you can keep doing it to the same tablet. You don't destroy it as you do this and that will give you different sorts of information than we are used to seeing as well. But I take your point. I will repeat one of the comments I made yesterday, if people decide what they want to measure then nowadays there is usually a way to do it.

DR. HUSSAIN: I think I share the enthusiasm. We actually have a project in our labs looking at stability using some of these things too.

DR. WOLD: Svante Wold from the chemometrics subgroup. We had a discussion about the specifications in our group and I had a different opinion than the others. I want to iterate that here. That is, if during development,

for instance with the blender, you find that this product with these raw materials, crystal size and all these things, mixes well in 15 minutes, of course, you use PAT to follow and decide on these 15 minutes, plus or minus three minutes or so. Then, if later, one day it takes 30 minutes, that is an indication that there has been a change. So, you can still use the ordinary specification and statistical intervals, helped by PAT. But seeing the process as a soft sensor, when the process changes substantially, that indicates that something has happened upstream. If you go to the polymerization industry, or whatever, they use this in exactly the same way. And, I think it would be very dangerous to say we won't have any limits and just wait to see if it is mixed. So, you have to use ordinary limits but you are helped a lot by PAT.

DR. LAYLOFF: You mean you would use PAT to accumulate data on acceptable performance and you set some acceptance criteria around that, and if it is exceeded by a lower bound you would have some difference occur upstream.

DR. WOLD: Yes.

DR. LAYLOFF: And that difference should

be investigated.

DR. WOLD: Right.

DR. RUDD: If it helps, we did discuss that point in our group. You know, there is flexibility needed, and I think probably Judy brought this out, but we need some kind of predetermined window, exactly as Svante described. You know, you can't have infinite flexibility. When do you stop? So, it is about operating in a window and recognizing that if you have to deviate from that window you have a problem, but not working to a fixed point.

DR. HALE: I think there is another piece of this pie beyond just the sensor, testing and specifications, and that is the process itself. By implementing these technologies we have the potential to not only measure our current processes better but bring on line better and more appropriate processes for what we are trying to do. In the end, that may be the biggest advantage of doing this, that we could, at the design stage, implement appropriate technologies that aren't constrained by our current momentum; that we can reconsider how we fundamentally design and manufacture processes. To me, that falls under the

encouragement category, that this technology sensing by itself gets us only so far but if we can implement a better way of doing things that can a dramatic leap and, to me, that should be encouraged and incorporated in the sensing and analysis section.

DR. LAYLOFF: Rule of the chair, we are going to skip the break and move on to Leon.

Process and Analytical Validation

DR. LACHMAN: In our working group we had a very interactive session and we had good representation from the regulatory group, both from the compliance point of view and also from the submissions group. So, we had a good dialogue and we have come up with some recommendations as to the purpose of the guidance as well as issues that should be included in the guidance.

[Slide]

The purpose of the guidance, from a validation point of view, is to expand the use of current and future process analytical technology for controlling of both batch and continuous production of existing and new products. That is the purpose of the guidance from validation's consideration.

[Slide]

Then we had various general guidance validation issues that were brought forth that the body of the guidance should consider. One is dealing with requirements for accepting PAT for conventional testing. What correlation is needed to replace current conventional testing? Utilization of PAT in current processes. How do we accomplish that? PAT as an "alert" in the use of old technology, out of trend versus OOS. We have certain limits now for dissolution or for content uniformity, for blend uniformity and those have been accepted for the product and are producing acceptable product with adequate quality and bioavailability, and now we have this PAT and it is going to provide us a narrower window than we are now using in the approved application. The concern is that the agency should not use that narrow window and forget about the approved specifications. We would suggest that this narrow window, as we develop this new technology, be used as an "alert" and the current window be used as the acceptance criteria.

[Slide]

PAT on-line to replace conventional

testing, identifying filing requirements if we change over to on-line controls versus the conventional testing controls. PAT as an endpoint can replace traditional endpoints such as time. We are not going to be using time as a controlling factor anymore because it goes away since this will be continuous data acquisition.

If sensors indicate improved process control, existing technology is accepted to meet current quality for release. What we are saying here, as we said previously, is that the currently accepted, approved specifications for product quality attributes will be the governing factor. The improvements, until they are finally worked out completely -- then there will be some changes made to show improved process controls and what will be submitted to the agency, and how we submit this will be subsequent interaction between agency and the people that are doing this new technology.

We were assured by the agency representatives that there is a group that has been formed, both from members of the compliance group as well as from the reviewing group that are actively pursuing this area, and they understand there will be education required for reviewing

people as well as for the field people to understand that as this technology is developed it should not be considered that we are having tighter specs and these should be replacing the approved specifications.

[Slide]

How to allow for improvement? The question is how do we go about this with regards to reviewing the improvements, self-assessing? Do we need approval or can we submit this as part of GMP that requires pretty much current good manufacturing practices; this can be considered GMP without a reviewing requirement.

New technology cannot delay time to market. We had considerable discussion regarding developing this new technology and we regards to filing, because here we are talking about economics and it is customary right now to have approval of your applications before the validation. The validation is subsequent to approval and it is part of the marketing requirement. So for the most part, the group felt that we should continue with the three batch initial filings because that is what is expected from us right now, and as the new technology develops this shouldn't delay the

marketing and we can always put that in the SUPAC as the product is on the market.

[Slide]

Dual development, we spoke about dual development, fast to the market with conventional testing and how this would switch over when the database is ready. Do we file both performance testing versus the current testing at filing? Do we file both or do we go ahead and finesse the performance testing and come in with a SUPAC filing once the product is already marketed based on the conventional three batch validation?

GMPs allow for process improvement, and the agency indicated that we are going to encourage ease of submissions of these PAT improvements as they become well developed.

[Slide]

Update of method/algorithm model more frequent than conventional, this may take place as we learn more of the performance evaluation. The methods should reference the validation guidelines including ICH. This was a suggestion by one of the members since this is currently being looked at by the reviewing group task force, and by referencing these guidelines, this indicates that this

particular guidance has already considered these and it is not intended to redo those guidances.

[Slide]

Here we talked about the validation of the continuous process and definition of batch size and impact of OOS. Here we discussed that the current approved specifications for a product for content uniformity or blend uniformity, the ranges that are approved in the application apply, and that the continuous process is intended to provide an alert currently until that has gone through a considerable amount of work and is finalized. So, the current process of reject or approval will be the current quality attributes that have been approved in the application.

Integration of unit operations into larger steps, it was felt that by using performance qualifications we could eliminate the individual unit operation testing. They can flow one into another and reduce the number of testing that we have to do even in performance assessments.

How process set points are treated in feedback loops, and this is something that we are going to be listening to the next speaker about when we talk about the use of statistics, math and

computer into the feedback mechanism for controlling a process.

[Slide]

The validation of the appropriate parameters will have to be defined as part of the modeling and development of the performance testing, and chemometrics is one approach and there are probably other approaches to data treatment that use different computer or statistical programs.

Those were essentially the issues that we came up with for consideration as part of the guidance document for the FDA group when they start drafting it from a validation consideration. Thank you.

Subcommittee Questions and Answers

DR. LAYLOFF: Any questions for Leon?

DR. BOEHLERT: Leon, I have a question for you regarding reference to ICH for validation of these technologies. Did your group feel that that would be adequate? Because ICH addresses the validation of small quantities of material, like milligrams of an active ingredient or small quantities of dosage form, and here we are talking about validation of technologies that are used in

very big containers or on-line, and I think there are different issues that are going to be involved.

DR. LACHMAN: I think what the suggestion was is to list the current guidelines that are available, ICH or FDA guidelines, so that we don't address those as part of the details that we will get into later on with this guidance. There is no doubt that the performance testing is going to be quite different than the individual testing.

DR. BOEHLERT: But even looking at accuracy, precision and some of these other measurements when you are talking about testing in kilograms in a blender may be different than they are when you are talking about testing small quantities of material, and I am just wondering if some guidance might not be necessary to avoid many, many different interpretations of how to accomplish this.

DR. LACHMAN: Well, I think what can come out of the details here could be a separate guidance, but I think the main purpose of referencing the present guidances was that these are available and what do we have to do to make the guidance either fit or change the current guidances. I think it is just a reference to what

is available. We don't have to redo those if they apply. If they don't apply, then we develop an appropriate guidance.

MR. HAMMOND: On the basis that a lot of the results that come out of this technology will be signatures rather than conventional concentration values, I don't see how the ICH guidelines can possibly fit.

DR. LACHMAN: It is not really to fit, it is just to list those guidances that are currently available, that have been used in the past for the conventional procedures. Really that is all it is.

DR. RUDD: We addressed this in a meeting in London, in October of last year, and we concluded that for process measurement the existing ICH documentation -- and you are quite right that we shouldn't reinvent the wheel; we should go with what is out there already -- but ICH documentation does not in any way address some of the peculiar issues of process measurement, and there really is a gap to fill. We sort of half attempted that from the meeting we had. We had sort of an arrogant idea of publishing something that could be a supplement to ICH. I think the key point is that the philosophy of ICH does apply, the general

concepts behind what I see ICH wrote I think are universally applicable. But there are clearly aspects to process measurement that are quite different. We don't want to reinvent the wheel but I think we should recognize here and now that there is a vacuum to fill and we would be well advised to fill it.

DR. LAYLOFF: I was just nodding in agreement with that. When you are looking at process assessments, the ICH is I think pretty much locked to the API univariant assessment of quality, and this is more looking at signatures, sometimes undefined signatures.

DR. LACHMAN: Well, it is an inference to the quality but it is undefined at some times too.

DR. RAJU: I notice that you have chemometrics there and that is going to be discussed in the next section, but chemometrics is there as data treatment and, since we are thinking of PAT in kind of a broad guideline which includes different kinds of physical and mathematical measures of measurement and chemometrics is positioned as an analysis that happens later, if you formulated in that sentence, say, independent of the different chemistry and physics of the

instrument, chemometrics is just another sensor, which is a mathematical instrument, and then the analysis fits into that framework and, just like physical and chemical, you now have mathematical sensors, what would be the problem of incorporating that in this framework in terms of validation?

DR. LACHMAN: Well, that was just one of the approaches. The other approach was to design the particular statistics and computer requirements for the feedback mechanism for the controlling of the process. Chemometrics was mentioned because that could be one component, one approach. That is all that is. It uses math; it uses some statistics.

DR. RAJU: But what if the math isn't a sensor?

DR. LACHMAN: Well, then we have a different approach. We don't use that approach.

DR. RAJU: You need a different approach then.

DR. LACHMAN: Yes, no question.

DR. LAYLOFF: We will move on to Mel who is going to give us the final answer, chemometrics.

Chemometrics

DR. M. KOCH: Thank you for that

introduction.

[Slide]

Let me just make a comment that was what I feel behind the introduction. It is perceived that I understand a lot about chemometrics because the center that I represent was one of those that started in the field. I work very closely with people who take chemometrics and have an impact on it. As a result, when we get into the details of what I am actually talking about, I have selected people in the audience who are going to stand up quickly and defend the positions and explain the reasoning. However, it is not hard at all to talk about this field, and it was mentioned that, okay, this comes now at the end of what you just heard.

In our working group we had a very difficult time finishing on time. We had no alternate subjects to get into. This is an emerging field, proven in other parts of industry at a minimum. It has gone far beyond curiosity in terms of mathematical techniques and is, indeed, showing results. I believe in some of the, say, reluctance by the statistician to look towards 6 sigma, tools like this take one along the road in designing for 6 sigma. So, we will move along on

some of this.

[Slide]

This is a little bit of a busy slide but it introduces some of the rationale for excitement in this particular field. The first parallelogram you see up there is a cycle. I call it developmental cycle and you can jump in at any point that you want, but to start with the reactor, the reactor pretty much represents, let's take, a process optimization as what we are now developing. The experiments that are being run, be it mini-reactors or other high throughput devices, it is generating samples. Those samples have to be analyzed, the data from those analyses evaluated, and then you get into your design of the next experiments and then continue on.

The DOE part of that, the experimental design is represented below in terms of some of our calometric terminology in that the DOE does require a number of pre-processing calibration diagnostic tools for eventual continuation of the process prediction and validation. A quick example of why all this will be important comes in -- let's just do process optimization again and we can borrow from industries that are well advanced in this

field and take the chemical industry, which is now using these cycles for catalyst evaluation, monomer preparation, a number of process parameter steps. In the operations within these labs, historically they have been running using process chemists, running several experiments a day and relying on well-equipped analytical labs to analyze the samples.

With the need to speed up development, time to market, improvements, etc., and reduction of cost, particularly capital costs as they are being translated to running pilot and development scale activities, we are running more and more reactors. We are now easily up to the hundred per day using high throughput approaches, which takes down the need for analysis. You need to do analysis every ten minutes. As this continues to grow, you no longer have time to send things to a lab. You have to make fast decisions. You have to extract things from your analytical profiles. You probably don't have time to do full spectrum or chromatographic separations but you have to quickly pull from pieces of that analytical data, which is use of chemometric technology. So, it is not as if one is trying to think of where we can apply it; it

is going to be forced very quickly and let's just assume it is going to be a part of everybody's program.

[Slide]

The role of chemometrics in the application of the PAT as we are seeing it is the application of sound mathematical and statistical tools requiring chemical knowledge. This is kind of a distillation of a number of definitions that Jerry gave yesterday, but we are trying to emphasize that the chemist is in a position to understand the statistics rather than to have a statistician come in and try to understand the chemistry that has just been applied here.

[Slide]

How do we see the role of chemometrics more broadly? This is a little bit out of order but it really comes down to monitoring modeling and control, the key aspects. In the monitoring phase we are trying to support the process through the use of the analyzers and sensors and effective calibration, and building models as a result that are deterministic and help us in identifying and deriving the state of the process, and then on to control to actively manipulate the process to

maintain a desired condition.

Very important in all of this is the fact that diagnostics are needed in each one of these steps. Some of you have probably interacted with production people, and any time there is something close to an upset, the sensor is pulled out first and somebody is accused of not getting the right measurement, and long down the list is perhaps that the process has gone bad. So, diagnostics are really to show the status of the instrument and how close it is to defining that which it was intended to do, together with the use of chemometrics to evaluate then the process and to have mechanisms for the feed forward of the results.

[Slide]

Now we are progressing along. If you would refer to the questions that we were given as a working group, I think we have defined now the role of the chemometrics and we get into what are some of the tools that are going to be needed. This is certainly not an all-inclusive list, but if one has a full grasp of this list you are probably in good shape to start seeing the results, things like the pre-processing; regression tools; the classification discrimination; outlier detection

and that comes back later in terms of how do you effectively gather outliers when you are trying to run a process in compliance; the homogeneity checking; the design of the next experimentation; and the data visualization; and although it is at the bottom of the list, very, very important is to make sure that there is some kind of uniform understanding of the terminology. This is an interdisciplinary concern. It even goes beyond the PAT that we are talking about, but we are dangerously close to having production folks, developing folks and discovery people all trying to use similar approaches and at times you can have similar approaches used by different disciplines and mixing in terms of what it is you are really trying to do. I am seeing a lot of that just in the process analyzer world where what an engineer thinks you said isn't quite what the measurement scientist said or meant. So, terminology is important.

[Slide]

What is needed for successful PAT using chemometrics? Certainly adequate measurements with the knowledge and experiments that go along with that; representative samples, again knowledge and

design that is associated with it; adequate analysis with getting the proper clarity, the reproducibility and, hopefully, the transfer of the data and implications; adequate data management at pilot through production stages; and then the other points of validation, the standard reference samples, emphasizing again some of this auto-diagnostic capability.

[Slide]

What is needed to develop, validate and maintain a chemometric-based PAT? Overwhelmingly, it is quality data. If you want to get into this scenario we referred to yesterday of waiting three generations for the next time you have a chance to do something, you have to make sure you have quality data, and the instrumentation is well understood, the data sets are well presented, and then you begin to apply these techniques. You need it at the reference sample stage. You need it continually from the routine product. Then, the difficult one is you need this data from outliers, or something, to effectively use the tools and that presents some challenges within the industry.

[Slide]

Currently accepted tools in industry --

this is not all-encompassing but just referring back to some of what Jerry talked about yesterday, there are things unfolding in industry in general with the use of parametrics, some of the EMEA, etc. and the PASG, and then there are a few others that were in Jerry's presentation I believe, slides 22, 23 where you can get more data. Then, one of the other ongoing initiatives is something we talked about briefly yesterday, within CPAC we have started to pull together an approach to try to define minimal requirements for ruggedness and other things that one needs to address when taking chemometrics into a production environment.

[Slide]

One of the things that we see that is needed in validation is to make sure that we have both initial and ongoing validation approaches to assure that the DOE does lead to representative data, that measurements are adequate, process sampling and algorithms are okay; the same with model validation and then be in a mode where everything we are doing could be structured to be predictive in final product properties, process and control, and other things that relate to validation considerations.

[Slide]

One of the big topics that we found is once we identified what chemometrics was and its role in PAT, very quickly you can come to how are we going to effectively train people in understanding and applying this? There is certainly not an excess of folks who understand it, who can train in it and participate. So, we are encouraging the ongoing participation in these conferences, symposia and workshops in the field. More particularly, I think FDA needs to have in-house short courses for people who are available and, as much as possible, to make these case-study related so one sees a real result and a real problem addressed. Direct involvement with consortium, and we have at least three that jump up in CPAC and the MCEC at the University of Tennessee and the CPACT in the U.K. Those provide certainly a forum for discussion. Then you get to the next part. At least within CPAC we have a calometrics focus group which is multi-industry and has a lot of cross-talk and discussions and the source of initiatives like I mentioned earlier, in fact, this COLI or calometrics on-line initiative.

Industry perspective is needed within the

agency to better understand the background and training for people doing this, and it is always difficult but I think what has worked as quickly as possible being part of the training is important.

[Slide]

Recommendations -- and I don't know that I would say that this is all that we would recommend but coming up early are a look for general exemptions from reporting, the PAT data for batch records collected for the purpose of investigating new technologies, recommendation that the guidance evolve from very simple examples models towards those complex ones, and that chemometrics is a tool for the reviewer that could be explained as to its role in the guidance. I am not sure if that is a clear point but we will work on clarifying that. Then, make it an audit function versus a review function.

That is it, and I would encourage any questions, etc. I notice that people who are able to answer them are still in the room.

Subcommittee Questions and Answers

DR. LAYLOFF: Any questions or comments?

DR. HUSSAIN: I have a couple of comments. One is with respect to the design of the

experiments. For the sake of argument, if I use NIR-infrared as an example, what you learn from your development experiments, which should be design experiments, translating that to a larger scale creates problems. So, I think in terms of design of experiments you are actually limited in terms of developing this on a real large scale. There are limitations to that. How would one address that?

DR. WORKMAN: One of the issues we were discussing there is to make sure that you are following good science, not necessarily relating that to the practice of how you would follow the good science, but good science is that if you are calibrating a system, for example, you are interpolating within the concentration space, the multivariate space, and that you have that space well represented; it is homogeneous. Good experimental design requires that. Now, how you implement that is another issue but these kinds of things can be clearly specified.

Then, on the validation end also how you select validation tools that represent the extremes of the space and how you test your system to make sure that it is predicting well within the

interpolated space. So, that is more of a good science issue and how you would describe that.

DR. MORRIS: If I could interject, I agree. We sort of discussed this in the group too, but if your model isn't working, whether it is a chemometric model or a simpler model, then that tells you that you are not looking at the right things. That is what you want to know. That is exactly you want at that stage so that when you get to full scale, even if the coefficients change, you know you have the right eye ball, you are looking at the right part of the process in your development and in your manufacturing. I think it all comes back to that. So, it should work assuming that you don't have some innate problem otherwise.

DR. WORKMAN: Another piece of that is that also as you look at any unknown sample, you know where that sample is representative to your space. Is it outside the space or is it in a well represented space. So, the good science is there and it is describable.

DR. HUSSAIN: Just sort of an interesting number that I have in my mind is the extent of use of DOE in pharmaceutical development. Do you know

the number? Three percent of companies use DOE today. This was from a survey Prof. Shangraw had done sometime ago but I think the numbers are still accurate. So, design of experiments is something novel, although it is not novel outside the pharmaceutical field, so that is the challenge you are looking at.

DR. LAYLOFF: And you think you are going to ramp up into PAT?

[Laughter]

DR. HUSSAIN: No, I think the point I want to make here is in the sense of for application for PAT in terms of a number of things, at least when I was there with the chemometrics working group, we discussed this. For many applications you really don't need any modeling at all. So, you have a whole range of issues to deal with, and in some more complex ones is where you need modeling. I was talking to Doug Ellsworth and I think it was discussed in the validation group that for some of the more complex attributes where you are looking at the multivariate correlation, those will emerge over time when you have real-life data from your sensors being accumulated. I think that would sort of summarize what he just told me in terms of how

one could validate that using production information. I think that would be helpful.

MR. ELLSWORTH: Ajaz may have given me a bigger charge than I realized. No, I was reflecting to Ajaz the discussion that we had when we discussed do you really have to take things to failure to really understand what that PAT technology is showing you, and the point was that, no, you don't but oftentimes you are in a much narrower range than the regulatory range would be. We said that was okay, you could validate PAT within that narrower range, and if you saw trends or information -- I think that was captured on the slide -- things that were outside that PAT range are not really considered failures; they are considered alerts. That would trigger the use of conventional testing methodologies to determine if a product meets regulatory specifications, and would trigger -- I don't want to use the term investigation, but I think an assessment of the manufacturing process to see what has changed and what can be done to improve that process or get further control of it.

DR. HUSSAIN: Or, you are still within the specifications, you can update your model. That

expands the range of the model.

MR. FAMULARE: I think further than that, a discussion that came out of the validation group, and that was somewhat captured on the slide too by Leon, is that GMP allows for continuous improvement so that as these things are found you can react to them, do what is necessary or put in what is necessary under GMP and just move on. So, we want to make the path for doing that as smooth as possible. That was a good bit of the discussion that we had in our GMP group, and we wanted to be able to have the flexibility to make those process improvements without filing under GMP so long as it didn't involve a change in specification or a change in the basic principle of what the product was going to be versus the submission batch or the pivotal batch. But continuous process improvement should be a smoother process, we hope, under this than maybe the current paradigm and this, hopefully, will be part of the encouragement aspect of it.

DR. MORRIS: Referring to something you had said earlier, Ajaz, whether you are using chemometrics or not, you are always using a model. It may be a linear relationship or something, but

you have to have some model unless you are just, you know, saying is it there. That is the only thing you don't need a model for in the statistical sense. But there is also the physical model, which is the physics or physical chemistry-based model, and the knowledge of that will always help design the other model that you are looking at if you know that there is a physical basis. So, just a clarification.

DR. HUSSAIN: The point I was making is that even the simplest design of an experiment, with the number of factors we deal with, I think it is impractical in the sense of pharmaceutical products. So, I don't want to put that as sort of a requirement that the design of an experiment is the only way out of this.

DR. MORRIS: Yes, and it is certainly not a way to identify variables that you haven't identified already. You can't design an experiment to come up with that. I don't know, maybe you should comment on that.

MR. LEIPER: I think the point that Ajaz makes is a very interesting one, and that is one of the reasons that one might ultimately want to go to continuous processing because, obviously, a time

slice is representative of that process and we can get the dimensionality into a time slice that we can't get in scaling-up processes. Of course, the scaling-up that we do in processes now is a gross risk because we don't know what the critical parameters are anyway. So, there are probably an awful lot of good ways around this if we care to take the time to think it through. DR. WOLD: To continue the discussion on experimental design, I think there is a general misconception that design of experiments applies when you have three, four or five factors, or so on, that they should be temperature, and pressure, and pH. But there has been an enormous development within chemometrics but also in statistics on the experimental design, and there is a large number of different approaches to deal with as complex issues as you want.

But to go back to the practical issues, in this discussion group we did not mean that you should take the results of a design, let's say, in lab scale and start to apply that in production scale. What we meant is that whenever you to experimentation, for instance, at least in Sweden when you put the process in use, before that you have to do robustness studies and some kind of

validation. It pays a lot to do both of those in a designed way. You save experiments; you get much more information and the factors you change are those that you know from development, knowledge and so forth that they influence the process. But robustness means that you ensure that when you change them within your controlled region not much happens to the results. Now, if you do that in a designed way you have a very, very nice basis for calibrating your chemometrics models because you have expanded the space that you are interested in. Of course, there will be a lot of additional factors downstream that result in what you do upstream, and those you can't control but you can still include them in the modeling.

DR. HUSSAIN: Just to clarify my point in the sense that if you look at my publications before I came to FDA, the are all statistical design of experiments because that is what I was pushing for at that time, and I am still pushing for it but I am being pragmatic and I just want to keep on the table the extreme range of options that we have to bring this technology successfully in. I just don't want to have the impression that this is the only one way of doing that. That is the

point I was trying to make. I am a proponent for design of experiments, especially in pharmaceutical development, because I use the phrase "I know it when I see it" and I think the way we set specifications, we have very little information really to set those specifications currently. If we have the design of experiments, we can not only have wider specifications which are relevant and, at the same time, you already have the concept of making your own SUPAC. You know you have a value or you have a range of values that your specifications are final and related back to your process or formulation variable. That is the advantage, but the reality is that the use of sound experimental designs is not prevalent in this industry.

DR. WORKMAN: If it would be helpful, we could call it a cookbook approach, but I think one of the issues is that without the design of an experiment you can't treat the PAT as a black box at all. You really have to describe everything you are doing.

DR. HUSSAIN: I think Tom raised the consistency. I think how you use the tool for, what purpose you use the tool for has to be kept in

mind.

DR. RAJU: Tom, one of the recommendations of the chemometrics subcommittee, the first recommendation was a general exemption from reporting PAT data to the batch records collected for the purposes of investigating new technologies. Does that fit already into the CGMPs guidelines and it doesn't need to be pursued further?

MR. FAMULARE: In terms of collecting additional data in the CGMP guidelines, I think we discussed some of that in our validation group, if that data is there it is part of the record. Whether it is in with the batch record or as a separate set of records, the physical location of the records is not that important. If the investigator sees it, I think the important thing is to look at is if it is part of the process improvement. That is going to be a key part of our training as we work with compliance and field people. Again, I have probably said this three times, as Ajaz started out in his slides, we are taking what we have now as adequate for intended use. So, as we learn more and we record more and it shows a variable we will allow for flexibility to deal with those variables. Over time, the hope

of this whole thing is that the company will improve their process and eliminate the chance for out of specification results, recalls, etc. because this will be plowed into good use, this data, and be able to better control the process. But a process that is already established under the existing paradigm as acceptable will stay that way.

MR. COOLEY: I think the concern with what we discussed and why we put that point in is because there have been some behaviors out in the field that would indicate that is not the case. You know, there is a concern I think in industry in general that that data will be used against us somehow rather than be looked on as positive, that you are trying to improve your process. The reason it was put in there the way it was is that if it could be exempted from examination, then that may make the industry a lot more open to experimenting with these technologies, particularly on existing processes.

MR. FAMULARE: The data that is generated in a company in terms of exempting that data or putting it somewhere an investigator can't see it is a hard thing to parse out in a guidance. I can only think of one example where, in a compliance

policy guide, we asked that internal self-audits not be reviewed by FDA even though they have the regulatory ability to do so. In this case, to take data relevant to a batch and to somehow deny it to an investigator -- I don't think there is going to be a proactive approach or will bring the investigator up to where we want the investigator to be in accepting and learning about this data and working with it. That approach would, to me, indicate that, well, we will just deny the investigator access to that information and I don't think that is going to be proactive in the long run, or positive.

The key is that as we write this guidance we also have to give this guidance to the field, and Doug has already taken on that responsibility with Mike Olson, to make sure that they understand that this is part of process improvement. We are not taking away the processes as they exist now. I understand the concern. It is going to have to be a strong element of the training. Doug may want to add to that.

MR. ELLSWORTH: Yes, I think I have to echo what Joe is saying. Would we never, ever look at that data and conclude that there is a problem

with the manufacturing process? I can't say no, but I think that if there is a conclusion that these data show that there is a problem, what we have to do is make sure that is not an independent judgment made by an investigator. That has to be a collaborative judgment made between CDER, the field and the firm that is involved. But I think for a general purpose we are going to want to see process improvement and try not to inhibit that.

MR. COOLEY: To clarify what we are trying to say, if you put an analyzer on-line there is some period of time that you are going to go through, particularly with the chemometric model where you are developing that model and you have not validated that analyzer. So, the data may not be an accurate reflection of what is going on in the process. That was the concern. Could that ultimately be used against a company?

MR. ELLSWORTH: The answer should be no, and I think we will have to make sure that that is part of the training, not just training but put it into our documents and directives that are issued so that it is memorialized in some policy statement.

DR. SHEK: I am not sure whether it is

chemometrics or validation, but as I was listening to the discussion here and talking about the scalability, I mean, that is basically the trick in the industry. We would like to do it in a five, ten liter granulator and be able to know that in 1200 it will work the same way. The issue in looking at PAT and whether the technologies is already there, can we, for example, if we position the sensors in a 5 or 10 liters or 75, do we know where to position them in 1200? Which means do the data that we collect on a small scale correlate on a large scale? I don't know if people would like to comment whether the technology is there so that at least we can compare data.

DR. RUDD: I can offer a comment. Positioning sensors is actually one of the things we addressed in the validation meeting that I referred to earlier. I think it is a characteristic of PAT measurement technologies that is different to laboratory based technologies. It is one of the things you have to go through during the validation of the methodology. Clearly, in order to validate the methodology you need to know the endpoint you are working to, and it is back to the process signature. That, to me, is the crux of

the whole thing, knowing what it is you ar trying to achieve so that when you transfer scale one of the things you do to validate your methodology of that new scale is to look at the influence of, for example, sensor position in order to recreate the signature you are talking about.

DR. SHEK: And that might change from one product to another?

DR. RUDD: Yes, yes.

DR. SHEK: And change from a small mixer to a larger one?

DR. RUDD: Exactly, yes.

DR. MORRIS: But, Dave, a point you made actually during our committee meeting is that to the degree that you can use the information you got during one process. I mean, typically you will keep the same equipment, so the next time you go through it, even though there may be minor adjustments, if you have established from one product and you go from a given piece of equipment to a larger piece of equipment, at least you have some starting point for your product. I think that was the point you made during our meeting.

DR. RUDD: Yes. Could I just ask perhaps a question to the experts in the working group

about availability about chemometric tools, developing this idea of process signature perhaps will allow us to arrive at that broadly based on a combination of fairly diverse measurements, for example, you are going to develop the signature from a spectroscopic measurement, maybe an acoustic measurement, maybe some imaging data, maybe some traditional classical measurements, pH and so on, and so on. I just wonder if the chemometric tools are out there to allow this sort of combination of diverse measurement techniques to get an overall picture of the process signature, as we are calling it, or whether that is an area of research that we need to recognize before those tools become available. I don't know if anyone wants to pick up on that.

DR. LAYLOFF: The only way I have ever seen it is treating one homogeneous set at a time. I have never seen, you know, linking together diverse databases, except on bounds --

DR. RUDD: And I guess that is the major difference that we are talking about, combining diverse data sets here, apples and oranges and how it balances out.

DR. LAYLOFF: I think you are going to be

stuck with doing acceptance bounds on each segment of the signature.

DR. RUDD: My question is are we, or are there more sophisticated tools that are out there that we need to be more aware of?

DR. HUSSAIN: David, I don't think that is a limitation of the chemometrics, it is simply availability of data. I mean, all you are looking at are dependent and independent variables so you have to treat it that way.

DR. WORKMAN: Can I address that? I am sure Svante wants to say something but there are data augmentation methods and standard classical approaches are applied to two-dimensional image data. So, it is a basic chemometric problem, but data augmentation allows you just to string these things and deal with them, and to normalize the data so it has similar scales, and then to deal with it as a large segment.

DR. RUDD: I don't want to get stuck on a technical detail but I think we shouldn't underestimate the complexity of what we are trying to do. We are talking about, for example, spectroscopic data. We are talking about univariate measurements like pH and temperature.

We are talking about acoustic data where, you know, I showed some wavy lines yesterday and, you know, it is about feature detection from traces like that. It isn't as simple as looking at tables of Excel numbers.

DR. LAYLOFF: Svante has the answer up there.

DR. WOLD: Well, I am not sure about that. What we can say is that in about 1985 or so the problem arose. We started to have too many variable to put into one block. There is a variety of so-called hierarchical multivariate models where you put your different types of data into blocks, and then on a lower level you make some modeling of each block and then you take the resulting scores and carry them up to the higher level. There is nothing that prevents the blocks from overlapping and in that way see the information sifting in a more clear way. It solves this problem that, for instance, two or three univariate measurements will otherwise be masked by 300 NIR-infrared light results.

It has another advantage too, and that is if you have a model and you have 4000 FID measurements, you don't turn everything upside

down. You just add another block and it is a very mild operation.

DR. RUDD: All right. Forgive my ignorance. Thanks.

DR. LAYLOFF: That is why we came here.

DR. M. KOCH: I was just going to add that we are probably further towards being able to do all of that than we are in the limiting regard that you mentioned in terms of just the separateness. One of the other initiatives that we have undertaken at CPAC in conjunction with a food industry initiative is to try to develop algorithms on raw material quality and its effect, or the variations in raw material quality and its effect on final product properties. That is going to be adopting a lot of different technologies. That, coupled with some of the things that are going on with multi-dimensional chromatographies and other array approaches I think will put us further along that road than would initially be thought.

MR. CHISHOLM: I think, at the risk of people having to be here all afternoon and all evening, it leads me to reopen something. It is not just about not having enough data. One of the discussions that we had, and in fact one of the

things on the overhead which I thought would provoke questions from the whole team was that a) we mustn't threaten time to market under any circumstances and, b) this means that we may have to go back and still submit three validation batches. I thought that would bring gasps of concern because, obviously, if you do that you are sticking with the old methodology before you move to the new.

So, in terms of such predictive technologies and lack of data, when we try to make a submission how do we get around not having enough statistical data to actually persuade the agency that we can, in fact, go ahead and do it the new way because we will not have enough statistical data? I think in terms of validation, that is probably one of the most significant questions because time to market will be a big driver in stopping us from going ahead if we don't manage to get into some of these areas.

DR. HUSSAIN: To respond to that, in that case PAT becomes a post-approval activity.

MR. CHISHOLM: We may have to face up to that. I am trying to be realistic. I don't know the answer to it, but I just wonder if in anyone

has any ideas about it because we didn't come up with an answer in the validation group, and one of the things you asked us to do, Ajaz, was to come up with stoppers. Well, that is a pretty big one if we don't solve it.

DR. LAYLOFF: Deathly silence!

DR. HUSSAIN: I think the solution has to come from you, not from us.

MR. CHISHOLM: I am just an engineer!

MR. FAMULARE: We had the discussion, Ajaz. This was a good point brought up by Bob, and Bob felt that the regulators would want to see PAT development from beginning to end in the process and in scale-up and validation. The one thing that I tried to emphasize is that validation in and of itself is a post-approval activity. So, we wouldn't want to hold up approval based on validation. Then, all right, the product is approved and if time to market is longer using PAT versus doing three batches under the conventional methods, well, that will be a discouraging factor to companies. Until such time as data can be developed for PAT, it may be a dual approach. They may use their three batches to get to market, but then move ahead with PAT, and PAT at some point may

overtake what was the conventional validation. But not all of this is beyond the filing realm and the flexibility should be there for companies to do so.

DR. DEAN: I would like to come to your point, Bob. I don't think this is an answer to it but perhaps another perspective. I think the way we currently do these things, there is a functional separation between the people that are trying to get a product to market and the people that are trying to produce it at commercial scale afterwards. As long as that separation is there, that is a problem to sacrifice time to market for potential benefits that are further downstream. We have seen some cases of organizations taking an interesting step to give life cycle responsibility for cost structures in an operational environment that really cut across some of these organizational, functionally oriented structures that currently exist. When you do that, you actually have the possibility to look at the trade-off between time and getting it better. You know, it is not always clear what the right thing to do is, but at least then you have some degree of accountability and someone who is tasked with making that evaluation. Right now it really

doesn't happen and you have the situation that you are talking about where time to market is never compromised, and there may be cases where it would be good to do so.

DR. KIBBE: In fact, the dollars push towards avoiding anything that slows you on an innovative scale, but we can look at different segments of industry and imagine different segments being interested in PAT at different stages in the development. A company that has a lot of mature products on the marketplace might see a real benefit for going forward in terms of cost containment. In a competitive arena generic companies would gain a strong advantage in terms of cost containment as a way of fighting out in the commodity market and, yet, the innovators might still view the risk adversely in terms of first to market. I don't know whether we can change that with a regulation.

I think that is the single biggest barrier that we talked about in our group to fully implementing PAT as drugs are going through method development or development stages for a new drug entity. What we also see internationally is that companies go to market first some place else. If

that is the case, and that environment allows them to go to market with PAT already fully developed, our willingness on this side of the world, the United States, to accept PAT as part of the submission will just make it that much easier for them in the long run.

So, all of those factors are in place and we can't control all of them, and there is no use us addressing all of them but we certainly can make the environment here friendly and encouraging for people to go to PAT.

I think the other thing is that as long as the spirit of the regulation and guidelines are to encourage, as problems come up with individual submissions or individual companies with individual products, if they find an encouraging and open environment within the agency it is going to promote them taking a little bit more risk in terms of first to market or first on the shelf.

DR. LAYLOFF: Svante says he has one small comment, and this is the last point on the discussions.

DR. WOLD: I would just point out that you have now renamed yourself to post-approval technology committee. PAT has a new meaning.

DR. LAYLOFF: Okay, Ajaz? While Ajaz is getting ready, is it possible for each of the working groups to get copies of each other's slides?

MS. REEDY: They will be on the web site by Friday.

DR. LAYLOFF: Thank you.

Summary

DR. HUSSAIN: Well, two days have passed and I think the discussion would have continued. I am pretty excited to give the closing remarks. Trying to reflect back, I went to my office to try and put some of this together and I was a bit apprehensive about what will come out of these working groups. That was a bit scary to me but I am pleased with how things have turned out.

[Slide]

The question was why are we here, I think from my perspective, to find a better way to sell to our customers. I think industry and FDA have one common customer and that is the U.S. patients. We wanted to do this by improving our manufacturing and also associated regulatory processes. In some way, we did a gap analysis, at least in some parts of the meeting early on.

We wanted to build some consensus on better understanding the potential role PAT can play, and also to come on the same page to some degree. I was talking to Ken Leiper and he said, come on the same page? We will be happy if we come in the same book. But based on the summaries that we have seen, I think we do have consensus on the benefits. We did achieve a lot at this meeting. We wanted to identify real and perceived regulatory hurdles and initiate the process of finding solutions.

[Slide]

We didn't come here to do this. I don't know if you can read this, "unable to determine the structure of this byproduct by spectroscopic method -- you are worthless; you will never amount to anything!" So, we are not here to do this. This comes from the chemical innovation journal. I thought that was interesting but we didn't do this. I was very pleased to see that.

[Slide]

Expectations and challenge at the end of this meeting, in my opening remarks I said we expect to have topics covered in the guidance, some sort of an outline; lay out general principles for

setting specifications, validation and chemometrics; and consensus on benefits, definitions and terminology. That is work we wanted to achieve. Listening to the discussion and the summary presentations, I think we did that. You can correct me if I am wrong in my assessment of that.

The challenge I have seen was that we come from different perspectives, expertise and affiliations and I was worried about this issue, can we come to the same page at the end of this meeting. Again, you will correct me if I am wrong but I think we did. I think we are on the same page; not in the same book, on the same page.

[Slide]

So, I think we have accomplished what we started to do, and that leads to my sense of PAT. After listening to the discussion, I was not expecting you to change the definition or the name but I thought I would let you make the proposal so this is not exactly what one of the groups made the presentation on.

In listening to the discussions, I felt that in my mind PAT are tools and systems that utilize real-time measurements, or rapid

measurements using processing of evolving quality and performance attributes of in-process materials to provide information to ensure optima processing to produce final product that consistently conforms to established quality and performance. It is a bit wordy but I think that is my sort of take-home of how PAT is starting from the definition I gave you at the beginning of the meeting. It is not perfect; it needs polishing but I will look at the definition you have prepared and see whether we can merge the two.

[Slide]

I still think options for introducing PAT, the three I mentioned earlier, are still valid and I think we need to have a guidance that covers existing products in sort of a post-approval activity to new products, and I think we need to have a broad guidance that allows for these options to be utilized by the industry.

The one which I labeled (b) where you have current manufacturing problems is an opportunity to improve, and to improve not only by trying to understand your process better, not just tweaking the process and hoping the auto-specification rate goes down. So, I think in the current situation

with the high level of manufacturing difficulties that companies are having, option (b) is really an option. But I believe all three options should be considered and are useful for the guidance.

[Slide]

Next steps, we have to report back to the parent committee so we will have a report on our activities here at the next advisory committee for pharmaceutical science. The meeting dates are May 7 and 8. I think Tom will make that presentation, but we have Art and a number of people from that subcommittee already here so the group will make the presentation to the parent committee.

We plan to have a subcommittee meeting in June. I don't have a date yet. I was hoping to give you a date but I don't have a date, but we are aiming for June, maybe the June-July time frame. We hope to have a more focused discussion because we intend to go back, reflect on this meeting, get the transcripts and study those transcripts very carefully, and come up with more focused questions for you. In fact, my hope is that we actually will have an internal draft before we come to you so that we know exactly what questions to ask and get you to give us some information that is useful for

us.

One thought in my mind was if we can have a real-life example, if we can sort of go through one example of a PAT application, that might be helpful. There is a question mark there because I don't know whether that is feasible or not.

As you leave, I would like you to think about what we need to do to prepare for the second meeting. One aspect which I would ask you to do is to seek input from your other colleagues within the company so that you start bringing them in and start bringing their questions to the meeting also. I think this was a very good start, not only for the information we received but I saw the participation of our FDA colleagues and you saw it too. I think we are working together as a team internally and with you, on the external side, and so the possibilities and opportunities are great and we have to move forward beyond this. But give some thought to what you think you could do to prepare for the second meeting. Please feel free to share your thoughts with us on how we can improve the second meeting agenda. you have my email, or you can send email to PAT@CDER.FDA.Gov. So you have a simple email address for PAT and we

will prepare for that.

[Slide]

I will end my presentation with what I think is a win-win solution and what each of us has to do to create that win-win. From an FDA perspective, we are not going to bring the technology. All we will be doing is provide an unambiguous regulatory process for PAT. That is what we can do. We can't do more than that. So, the general guidance for industry will articulate the regulatory position on PAT, our expectations and the regulatory process. That is what the guidance will do.

In doing so, we are collaborating with industry and academia at this meeting and in other arenas too. I have also talked about the second track. We want to work with companies which have done this so that we can bring information, train our trainers internally and work with companies to do that.

Industry has to do several things for this win-win. It has to have the willingness to improve and change. There are many challenges. I think manufacturing is generally on the radar screen of the higher CEOs and so forth. I think

manufacturing needs to be recognized as an important function. Some companies do and some companies will not. Manufacturing is a side that could be contracted out. So, I think you will see different perspectives on that but I think companies that do recognize manufacturing as an important activity really are the ones which will, I believe, bring PAT into existence. I think you have the technology know-how and I think good science is what you need to develop and apply in your submissions and, again, collaborate with us on how to move this forward.

Academia plays a very important role. We do need knowledge, especially in the public domain, so that not only we understand things better but we make sure the field grows as it is supposed to, and also future experts and leaders will come from students who are probably just entering chemistry programs.

With that, I really wish to thank you all for your contribution. This has been a great experience and I actually was apprehensive about how this would come out. My feeling is that I think it came out extremely well and useful for us. I hope you will agree with that. Thank you very

much.

DR. LAYLOFF: I also would like to thank the presenters, Art, Judy, Leon and Mel for making the presentations, organizing their presentations and sessions. I would like to thank my former FDA colleagues for their openness, attendance and participation. I found it quite exciting. Of course, maybe something is wrong with me. Anyhow, the meeting is adjourned. Thank you very much. Don't forget, send your comments to PAT@CDER.FDA.gov. Thank you.

[Whereupon, at 3:45 p.m. the proceedings were adjourned.]

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