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PROCESS ANALYTICAL TECHNOLOGIES (PAT) SUBCOMMITTEE OF THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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wtk

P A R T I C I P A N T S

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Ronald W. Miller, Ph.D.
David Richard Rudd, Ph.D
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Jozef H. M. T. Timmermans, Ph.D.
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Justin O. Neway, Ph.D.
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C O N T E N T S

P R O C E E D I N G S

DR. LAYLOFF: Okay. Kathleen told me it's time to get started, and you know how Kathleen is. First of all, I'd like to welcome you all to our second meeting of the Process Analytical Technologies Subcommittee. It's a pleasure to be here with you all to talk about new and exciting toys for big boys--new technologies, one of my favorites. And before we get started, Kathleen's going to read to us the Meeting Statement.

MS. REEDY: Acknowledgment related to general matters waivers for the Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science, June 12, 2002.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The Food and Drug Administration has prepared general matters waivers for the following special Government employees which permits them to participate in today's discussions: Dr. Judy Boehlert and Dr. Melvin Koch.

A copy of the waiver statements may be

obtained by submitting a written request to the agency's Freedom of Information Office, Rom 12A-30 of the Parklawn Building.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they may apply to the general topics at hand. Because general topics impact 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 Dr. Efraim Shek, of Abbott Laboratories, is participating in this meeting as an industry representative, acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

With respect to FDA's invited guests,

there are reported interests that we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Leon Lachman is president of Lachman Consultants Services, Incorporated, a firm which provides consulting services to pharmaceutical and allied industries.

Dr. Howard Mark serves as a consultant for Purdue Pharma Incorporated.

Dr. Kenneth Morris serves as a consultant, speaker, researcher, and has contracts and grants from multiple pharmaceutical companies.

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

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

DR. LAYLOFF: Okay. Thank you, Kathleen.

I'd like to no go around the table and have you introduce yourself and your affiliation.

We'll start with John James.

DR. JAMES: Yes, good morning. My name is John James. I'm the Executive Director of Operations Services for Teva Pharmaceuticals.

DR. SHABUSHNIG: Good morning. I'm John Shabushnig, and I'm the Director of the Center for Advanced Sterile Technology at Pharmacia Corporation.

MR. COOLEY: Good morning. Rick Cooley, process analytical chemist with the Management Technology Group of Eli Lilly and Company.

MR. WALTERS: Good morning. I'm Colin Walters, Schering-Plough Product Optimization. I'm a senior engineer.

MR. CHISHOLM: Good morning. I'm Bob Chisholm of AstraZeneca International, Technology Manager based in the U.K.

MR. WETSTONE: Good morning. I'm James Wetstone, the Chief of the Process Measurements Division of the National Institute of Standards and Technology.

DR. TIMMERMANS: Good morning. Jozef Timmermans from Merck and Company, Manager of the Pharmaceutical Technical Operations Group at West Point.

DR. WORKMAN: Good morning. Jerry Workman, Senior Research Fellow of Kimberly-Clark in Wisconsin.

MS. SEKULIC: Good morning. I'm Sonja Sekulic, Assistant Director, Technology Development at Pfizer in Groton, Connecticut.

DR. RUDD: Good morning. David Rudd from Process Technology in the Pharmaceutical Development Group in GlaxoSmithKline in the U.K.

DR. MILLER: Good morning. Ron Miller, Principal Technology Fellow, Bristol-Myers Squibb.

DR. SHEK: Good morning. Efraim Shek, Divisional Vice President for Pharmaceutical and Analytical R and D, Abbott Labs.

DR. ANDERSON: Good morning. Gloria Anderson, Gallery Professor of Chemistry, Morris Brown College, Atlanta, Georgia.

DR. KIBBE: Good morning. Art Kibbe, Professor of Pharmaceutics and Chair of the department, Wilkes University.

MS. REEDY: Kathleen Reedy, Food and Drug Administration.

DR. LAYLOFF: I'm Tom Layloff and I'm an SGE with FDA, but my day job is with Management Sciences for Health and International

Pharmaceutical Regulation.

DR. BOEHLERT: Judy Boehlert. I have my own consulting business, consulting in the areas of quality, regulatory affairs, and product development.

DR. KOCH: Good morning. Mel Koch, Director of the Center for Process Analytical Chemistry at the University of Washington.

DR. SEVICK-MURACA: Eva Sevick with Texas A&M Department of Chemistry and Chemical Engineering and developing new technologies for blend content uniformity monitoring.

MR. HALE: Tom Hale, President, Hale Technologies.

DR. MORRIS: Ken Morris from Purdue University.

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

DR. CHIU: Yuan-yuan Chiu, Director, Office of New Drug Chemistry, FDA.

MR. ELLSWORTH: Doug Ellsworth, Office of Regulatory Affairs, FDA.

DR. LAYLOFF: Thank you very much and we'll now turn to Dr. Ajaz Hussain. Ajaz, you're up.

DR. HUSSAIN: Good morning and welcome to the second meeting of the Subcommittee on PAT. My handout should be outside for those in the audience, and copies of the handouts have been distributed to the subcommittee this morning.

I just want to share with you some thoughts on how the goals and objectives of this meeting and share with you some progress we have made within the agency and where do we go from here.

I also wish to thank several invited guests whose names appear on the program, and others who will be speaking and will be participating, for example, from NIST and from Measurement and Control Engineering Center in Tennessee. Professor Kelsey Cook, I see him in the audience--there he is--and so we hope this will be an exciting program where we can brainstorm and bring a lot of information so that FDA can quickly, and as quickly as possible, develop a guidance on PAT.

For those who are attending this meeting for the first time, the goals and objectives of the FDA's initiative is to use PAT or Process Analytical Technologies as a model technological

opportunity to develop a regulatory framework to facilitate introduction of new manufacturing technologies that enhance process efficiencies and understanding. I think those are the two aspects which create the win/win from both public health, as well as industry perspective. With increased understanding of processes, we reduce the risk of poor process capabilities and so forth, at the same time increase process efficiencies.

The goals and objectives of the discussions today are to identify and eliminate perceived or real regulatory hurdles, and these are the goals for the general guidance that we are trying to develop. At the same time, we are trying to develop a dynamic, team-based, scientific approach for regulatory assessment--a review and inspection team for these new technologies. I'm pleased to let you know that we have essentially assembled this team of reviewers and inspectors, and some of them will be participating in this meeting also.

And also, last--but not the least--I think we have to start moving and thinking about international harmonization. EMEA, CPMP have issued a guidance in September on parametric

release which has certain bearing and certain commonalities with what we are trying to do here, but at the same time, I think there are significant fundamental differences that need to be identified and resolved. And some of that discussion will also happen today.

One question that comes up is why process analytical technologies? We believe process analytical chemistry has sort of matured and has proved its usefulness in many other industries but has not really been adopted in pharmaceuticals to a large degree.

We believe that PAT provides an opportunity to move away from the current testing-to-document quality paradigm to a continuous quality-assurance paradigm that can improve our ability to ensure quality was built in or was by design, and we think this is the ultimate realization of the true spirit of cGMP.

One of the things which excites me personally with the PAT technologies is you actually bring physics and chemistry together to bear upon the measurements that you are dealing with. Traditionally, we look at--actually destroy the physical information by dissolving and then

doing an assay. So that's in my mind a significant advance with why PAT can help us.

We believe PATs--optimal use of PATs can provide greater insight and understanding of processes, bringing these technologies at or in line to measure performance attributes is a better approach than taking sampling--or taking samples and testing in the lab.

We also have the possibility of real-time or rapid feedback controls, which is generally not practiced in the manufacture of pharmaceuticals because this can allow us to focus on prevention; potential for significant reduction in production cycle time and, in parentheses, in development. I think this is one of the challenges that we face today with PAT. Many of the champions for PAT in pharmaceutical companies are in manufacturing. The R&D folks either have not embraced this to a degree or are, in fact, opposing it. And there are many reasons for that. In fact, one of the reasons is many of the formulation development folks probably do not have the level of understanding of what PATs can do for them. And they're so in tune to the traditional ways of making formulations that there really is an educational campaign that needs to occur.

But I think more importantly we minimize risk of poor process quality and reduce regulatory concerns. I don't have to sort of outline the regulatory concerns in the manufacturing areas. You see those examples on a daily basis. And my concern is with the crunch in development due to pressures of getting the product out at any cost is going to increase the problems in the future. If we don't bring new technology in, the manufacturing problems are on the increase.

The strategy we adopted was a win/win situation. We wanted to create a win for industry, a win for public health. And we approached this with input from the Advisory Committee for Pharmaceutical Science, the parent committee of this subcommittee, and also the FDA Science Board. And the reason for the Science Board was to bring a high level of scrutiny as we develop this program, because in some ways this is a paradigm shift from a regulatory perspective. And you need all of FDA to be part of this, not just the Center for Drugs.

We have established internal collaboration between CDER and ORA. We have a PAT steering committee. The external collaboration, in my mind, is this committee. And, hopefully, in the future

we'll use PQRI to some degree for this.

We are moving down two parallel tracks. Track 1 is a general guidance on PATs, not focused on any technology, per se. The intention is to simply bring common terminology, as well as provide guidance on a regulatory process for bringing PATs in a regulatory framework.

You could imagine this guidance as Chapter 1, introductory chapter to a book if you are writing a book on PAT. What it means is, subsequently, we will have other chapters, other guidances, more technical guidances as we gather more information and we are able to write those technical guidances.

We are encouraging submissions now. And we are planning to have a team approach for review and inspection for these submissions. I am pleased to say we already have one submitted and in terms of a company has already come forward. The second company is working towards that, so we have two companies which have expressed interest.

A progress report could be sort of looked upon as the meetings that we have had. The first meeting on PAT was on the 19th of July 2001, then the 16th of November FDA Science Board meeting.

One of the major aspects of discussion here was that PATs need to be voluntary. These need not--these would not be a requirement. So a company can choose to use PATs, but it's not a requirement. So that was one of the fundamental aspects that we established with this meeting.

At the second Science Board meeting, we established the concept of a safe harbor or at least discussed the concept of a safe harbor, which I'm hoping that this committee will help us define it. I don't like the term "safe harbor" because--and I haven't used it in the questions that I framed to you, because I don't think we need a safe harbor. All we need is clarity of how regulatory decisions are made, and I think it will be fine. Personally, I don't like the term "safe harbor," but you could use it if you want to.

Now we are at the second meeting of the PAT Subcommittee. We originally had planned for only two meetings, but our task has sort of increased and we will have a third meeting of this committee.

Let me share with you the time lines. We are here today, the red arrow, the second subcommittee meeting, and the third subcommittee

meeting is being planned late September, early October, sometime on that time frame. We haven't even started discussing what exactly the date would be. What we hope to do is to gather information from you relevant for inclusion in our draft guidance, which we hope to have an internal draft ready--I can't commit to a release date, because that's totally not under our control--so we will have a working draft internally, which we hope to get out as soon as possible for public comment.

We would like to start our training program in October, and I look forward to receiving input from you on how we should structure the training program and the certification program. So that's sort of Track 1.

Track 2 is submissions now. The first company has come in, and that track essentially got started in May. So we are moving on Track 2 at the same time. Those small microphones or loudspeakers there, since we indicate a lot of the presentations that we do--I've lost track of the number of presentations I have done on this. It's sort of fallen through the track. I just wanted to emphasize I've been visiting companies like Aventis, BMS, Pfizer, AstraZeneca, and others,

trying to gather, you know, build consensus, as well as gather information of how best FDA should develop this guidance.

Let me briefly talk to you about Meeting 3. What will Meeting 3 focus on? One issue which we'll focus--we'll focus on a computer validation, including chemometrics part of it and Part 11 issues, because we still have a number of issues to resolve and we want to focus on those today and tomorrow, and Part 11 issues, computer validation issues, will be tabled for the next meeting.

Rapid microbial testing, we are sort of expanding the scope of tools that we use in PAT to include rapid microbial testing. And our Advisory Committee at the last meeting endorsed that that should be part of this. We don't have all the talents, scientific expertise on this committee to handle all the microbial issues, so we plan to use the third meeting and include some more members from microbiology to participate in that meeting to see how rapid microbial testing could be part of the PAT initiative.

The third thing which I would like to do--and I need your help for that--is at the third meeting, I would like to have a dry run. What I

mean by dry run is using a mock application submission inspection. Can we use an afternoon session and actually walk through a submission and the review and inspection questions that could come from that?

I need your help because I think I'll need you to help me create that mock application and so forth. So, please give me your suggestions on how we could do this. What I'm hoping is we could focus on maybe two case studies: a drug substance manufacturer, we could use online GC or HPLC as a model or a Raman technique. And go through that process and see what are the things that we haven't addressed should be addressed in the draft guidance. And for drug product, what I'm suggesting is we could use online NIR infrared for blending, drying and so forth, to create that mock example and walk through that.

So, today, day one of this meeting, we have clearly defined the questions for the subcommittee. It's in your handout packet. We have provided for you our current thinking and posed those questions. And these questions deal with regulatory uncertainty or risk and how best to address those. So most of the meeting today would

focus on those questions.

But we have left the questions undefined for the working groups. I'm hoping that you will frame those questions toward the end of this day and how we want to manage the working groups. And we have built in flexibility. We were planning two working groups: one on validation, one on development. But, for example, if we need a third working group on training and education, we could have that group as a possibility, or a fourth working group, so we have accommodations available. I'll look for your input on how best to manage day two.

In my handout, the last page, for example, is a set of questions that we received from Jozef Timmermans from Merck, of what Merck thought were the questions relevant for validation. So you have those set of questions for the validation group, and I'll also pose some additional questions here. But towards the end of this day, if we can sort of refocus those questions and come to some agreement of how, what are the most important questions to discuss.

Training and certification program is an important topic, and we really look for some

feedback from you, and then we'll identify questions for in-depth discussions by the working groups on day two.

Process validation working group definitely will be in this room. We will have--that probably will be the biggest working group. Product and process development working group would also be--definitely be there, but other working groups could be training and certification and possibly a regulatory process. I'm excited to see, you know, Jeff and others from Regulatory Affairs who have joined in. So that could stimulate some of the discussion that if possible.

For example, I think, the questions that we had in mind for the working groups, I'll just lay them out for your consideration.

Please identify and describe approaches for introducing PATs, for existing validated products, for new products. I mean the type of questions that we are--the type of information that we are looking for is some sort of a scenario of the steps necessary to do this and how the regulatory system should interface and when should it interface.

For example, PAT R&D efforts in pilot

plant, a company may start at the pilot plant to establish proof of concept and suitability for application in manufacturing. What should be documented to justify suitability? PAT R&D efforts could then move to manufacturing where you'd actually say, for example, blend--bring a blender with online NIR, same design and operating principle, and run that in parallel to your current manufacturing.

What should or would constitute acceptable verification of suitability and validation under that conditions? And once you have established that for routine manufacturing using PAT, what should be the regulatory standard for accepting an online measurement to replace end-product testing be?

What is the level of built-in redundancy? If the sensor fails, what is the backup for that? And then identify steps to resolve out-ofspecification observations. Under what conditions can end-product testing be used to resolve out-of-specification, because you are looking at a validated process in a traditional sense, why can't we use that as a backup system?

The distinction here I think you have to

pay attention to is the parametric release concept originally initiated from terminally sterilized parental product. Under that scenario, any deviation from the validation, sterility testing is not a viable option. You cannot rely on sterility testing to release a batch if something happens in your manufacturing. So, it's end of story then.

But PAT, in my mind, is somewhat different. So I think we have an opportunity to define under what circumstances end-product testing could then be a reliable way of resolving this. But I need your help to define that for us or sort of discuss that.

Continuing on, the questions for working groups from an FDA perspective. Using online NIR for blend drying, content, and dissolution and an HPLC as an example for PAT, please outline the essential experiments--what I mean by experiments is hypotheses or questions to be posed--that should be conducted by a company to successfully develop and validate these tools for use in manufacturing operations. I'm essentially setting up this for the next meeting.

What criteria should be used to ensure that relevant critical formulation/process

variables have been identified and appropriate PAT tools selected to ensure their optimal control?

What information should be collected to justify use of indirect measurements, such as signatures or correlations, that relate to product quality and performance attributes?

When and to what extent would FDA involvement facilitate PAT R&D and application projects? And so forth.

So those are sort of our suggestions, combined with the questions from Merck and questions that you have, that I think will frame the discussion for tomorrow.

I just want to emphasize again, sort of--but I want to end my presentation with just sort of a case study. The general guidance--I want to emphasize so that I'm not creating a high expectation. The general guidance is not a technology guidance. General principles and terminology is what we will focus on. Address issues related to regulatory uncertainty and clarify the regulatory process. We hope there are other tangible benefits: serve as a tool for building consensus, especially within-company consensus, and promote research and development in

this area.

Some thoughts on general principles and terminology. The first question that is posed to you in your handout is definition and scope of PAT. I think it's important to define that very carefully and clearly.

And, also, I'm asking you to sort of develop a shared vision for this group. What do you--what does PAT mean to you? What is the current state and what is the desired state you are trying to achieve using this new technology?

From my approach or from my thinking, the win/win comes from higher level of process understanding, functional or performance indicating process controls and specifications that we'll set using a systems approach; high level of process quality; minimal reliance on end-product testing; improve the scientific basis for regulatory functions; rational risk-based documentation requirements. And the point there I'm trying to make here is, currently, the current manufacturing paradigm essentially is the GMPs have to be very, very laborious and documentation is so critical because, in many cases, the manufacturing is a black box, and we rely on very limited end-product

testing just because of the extensive GMP documentation requirements we have.

Any deviation from that results in a problem. But now, when you make the process more transparent, what should the documentation be? And that's somewhat a Part 11 issue, also, that we'll discuss. But, also, clearly high efficiencies for all operations, from industry and FDA operations.

So, my thoughts on PAT, I see PAT as a tool in a whole quality system. And here is a quote from a book on total quality control which was published in '83, and it sort of charts out the evolution of quality systems in the U.S. In the 1900s we relied for quality only on the operator, then we added a foreman, then we added the concept of inspection, then we moved to statistical process controls in the '60s, and then we went through the concept in 1980 of total quality, now we generally talk about total quality management system.

And the point here I think is that "Real assurance of quality today requires far more than good intentions, testing and inspection activities, and a traditional quality-control department." This was said in 1980. "It takes the same business, managerial, and technical depth to assure

that the quality and quality cost of the product as it does to design, make, sell, and service the product itself - depth starts well before production begins and ends only with [customer satisfaction]."

What I see is PAT is a tool that enables us to move in this direction. Many have or some have argued that the pharmaceutical--there's no role of statistical process control in pharmaceutical manufacturing. You know, I read a book by John Sharp from the U.K., and it's a very well written book. I agree with all of the things he has said in that. But towards the end he said we are not making, you know, machines and so forth, so statistical process control has no role in pharmaceutical manufacturing. I said that's old thinking. And we'll leave it at that. So PAT is a tool that enables us to move in that direction.

A second sort of perspective on PAT is that if you look at the facts or the trends in quality, we started in the 1950s with sampling plants, then came the zero-defect movements in '60s, ISO-9000 in the '80s, you know, quality system 9000, Malcolm Baldrige Award, European Quality Award, total quality management. Now the

buzzword is Six Sigma and the buzzword has changed to Ultimate Six Sigma, and so forth.

The point here is GMPs came in at that point, and if we don't understand processes, all these are fad because what is--unless you understand the variability, the sources of variability, you really cannot improve quality, you cannot go to Six Sigma. And with the measurement systems we have, we don't have a hope of getting the pharmaceuticals in this direction. So that's what I see as PAT coming in to help us move in this direction.

Now, let me sort of end my presentation with this sort of a case study. The case study is a study that helps me look at PAT. And what I would like to do is take a case study which people consider as the most difficult case study. How would we do on or at-line assurance of acceptable dissolution rate? Okay? And it's a hypothetical case study, but with real data. And the real data is FDA data.

So now let's imagine dissolution of a tablet is a function of particle size of the drug, amount of excipient 1, amount of excipient 2, a process parameter 1, a process parameter 2, okay?

Process parameter 1 is, say, blend time. Process parameter 2 is a compression pressure or force, and you have an in-process test of hardness.

Currently, the way we assure quality is you have level 1 quality assurance, which is essentially the GMPs: specs of incoming materials, SOPs, process controls and so forth. And then level 2 quality assurances test conformance to dissolution specification and along with other specifications.

The data is real. Why I'm calling it a hypothetical case study is because we did this study in a retrospective fashion. We had just finished our manufacturing project at the University of Iowa. The drug is furosemide. And we had designed an experiment of different formulations and we were ready to do biostudy. So we wanted to link NIR infrared analysis to the biostudy because that is possible now because you're doing it nondestructively. So we can actually measure the amount of drug in a tablet and also estimate its dissolution rate before you give it to a patient. So that was the link. But here is for dissolution. I don't have the data for biostudy yet.

What we could do is take the NIR infrared spectra of a tablet, measure the dissolution of the same tablet, and establish a correlation. And here we have taken the entire spectra. And so you have an at-line tablet NIR spectra and a dissolution correlation. So you have a training set, which is the graph, and then you test how good this correlation is using a test set which is different. And what you see there is you have wonderful predictions and if the end-product testing is a one-point specification that Q is more than 80 percent dissolved or 70 percent dissolved in 30 minutes, there's no problem in meeting that requirement. But the concern I have is this is a black box. Validation of this is based now on predictive performance of the calibration. In fact, that would be probably equal in terms of regulatory requirements to what we do with in-between real correlation. If you look at our guidance, how do we make decisions to waive biostudies when you have a correlation that's based on predictive performance only?

So that type of correlation validation would be consistent with our current standard for waiver of biostudy. But I think we can go a step

better. What are the critical formulation variables in this? For this formulation, dissolution was predominantly affected by the disintegrant level and by interaction terms involving disintegrant and diluent and diluent and magnesium stearate, so, we know it was mainly composition based.

The hardness, the compression pressure really did not have an effect. And that's typical of formulations that contain a super disintegrant; you actually eliminate all the process variables because the super disintegrant takes over. So that's consistent with that mechanism. And when you do a modeling of those components and dissolution, you are able to explain 93 percent of the variability. So it's a fairly decent relationship between composition and dissolution.

So what we could do is here, I told you we have a black box, but the black box says it could be a hat trick and we could actually make it more transparent and make it more science-based. And now the proposal here is you can take the NIR infrared spectra, you know the critical variables, link those together. Can we measure those components? And we could. So you have taken a

step beyond a validation of correlation of a black box to something which is a meaningful link directly to the variables.

We did it at line. I don't see any problem doing this on line or even taking it further from behind. Using blend uniformity data and some tablet compression data you can actually do this. So, by doing this, I think what we have been able to sort of gather is these are pretty straightforward things to do. And all we need to do is make these available.

The challenge comes as--that was a small-scale study. We did that 3-kilogram or 5-kilogram batch. Then the question would come as, how, when you scale up. will that still remain? We didn't scale up in that--we did scale up but I didn't have the data on that one. We did scale up to 16 kilograms--but I'll show you a different example which showed the scale-up aspect.

Here is an example from Metoprolol tartrate and the box that you see on your left-hand side, upper side, is a designed experiment dissolution rate. And in this case, dissolution was a function of magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

We linked it to dissolution in bio, on the right-hand side. But this work was done on small scale at the University of Maryland as part of our SUPAC research program. We didn't stop there. We said, can we generalize that small data set to the submission data that we have in-house? So we took that information, developed a new network. This work was done by Vijet Damara [ph], who is now at Sanofi. He did that when he was a reviewer here. And he actually predicted what the dissolution should be of the generic tablets and the enumerator tablet from our submissions. For all but two, we could do that very, very well. And that took 10 minutes.

The two formulations that we were not able to, the difference was their ratio of sodium starch glycolate and mcc inside or outside. There were significant differences that it really didn't fit the pattern. But for the rest on, it did. So the scale-up could be sort of verified, that scale-up was not an issue. And we didn't have the NIR at that time but we could have connected it to that.

So, that's the concept. I think we need to understand that when we do experiments on a small scale, in the traditional way when we don't

have the right measurements, it's difficult to scale up rationally. And here is an example, I would like to use from Ken Morris and Purdue. When you do on-line analysis of blending and are able to gather information about the kinetics of blending, you can actually model and predict what the large scale should be. And Ken is here; he could talk to you about that, but he has done this only for drying and for blending.

So, with PAT, you are actually gathering far more scientific information to actually do rational scale-up and be predictive of what can happen, instead of saying, oh, the scale is not going to work.

I'll end my presentation with sort of built-in redundancy. I'd really like to have you think very differently about this. Redundancy need not mean two systems. For example, I have a NIR unit one which is measuring some attribute. We want to have a backup system for that. That doesn't mean that I have to have two NIR. The picture there shows different location of NIR for blending. That's only to illustrate that we don't need to have multiple sensors, but simply look at redundancy as a systems approach.

For example, when you look at a systems approach, the overall quality system is the first level of defense. Then comes product- specific SOPs, your raw material classification and so forth. That's your second parameter of defense. Once you get through that you have actually eliminated sort of variability. Then comes PAT and then comes so forth.

So, when you look at a systems approach that comes up with a thing that there are many tests, many measurements that actually overlap and you can actually use them as backup and need not be two separate systems. So, I think we have to start thinking about that in sort of different ways.

With that I'll stop and give it back to Tom.

DR. LAYLOFF: Thank you, Ajaz. It's a very exciting time. I think the last slide brought an interesting point. I think it's an aggregation of measurements that are critical to the product quality, not a single dimension at a point in time.

I think it's also very exciting that we're going to be doing microbiological tests because if you look at the chemical tests, it's fairly easy to see that you can change the technology without

changing the bar, but I'm not sure that--how difficult that's going to be with microbiological testing when you shift from microbial limits on plate counts to DNA or other technologies with it, but the bar may actually shift.

Anyhow, also, I think critical the critical issue is going to be for us is the training and certification. The competence of the reviewers and the investigators are going to be the keystone for this whole process. If we don't have well-trained reviewers and inspectors, this thing will not go well. So, your input as to content, structure, certification of competence are going to be really critical in how the FDA moves forward on this.

And as Ajaz mentioned, we've gone from four committees to two, but that's a flexible yardstick. We can move to back to four if we need it, and we'll look to you all for guidance as to whether we should increase the number of committees that we break down into for the guidance.

Now, we have the subcommittee discussion on training and--

DR. HUSSAIN: Why don't you go to the invited speakers and then--

DR. LAYLOFF: Okay, let's go with--okay, we'll change that around, okay. Let's go with Jeff, Jeff Blumenstein, from Pfizer, formerly FDA.

DR. BLUMENSTEIN: Thanks, Tom. We welcome the opportunity to share some thoughts today on PAT. Let's see, there we go. I'd like to present some perspectives about some regulatory challenges that may be relevant to PAT applications in new NDAs.

When we go forward and try to develop new NDAs, it's really, from our perspective, a balance of goals. You know, we're developing a new product and it's a balance of activities to try to meet mutual goals--designing the product and processes, the methods, as well as other goals like facilitating the rest of the program, the production of clinical supplies. And then, looking toward the commercialization, developing the process knowledge, transferring the technology. So it's a number of different drivers, and at the end of the day we're all trying to balance different things, like time, resources, and costs. With time, people, and money, we can always do everything, but at some point at the end of the day we've got budgets to maintain and time lines to try

to bring new products to market.

And that really is where the balance of goal comes about. First, trying to facilitate the commercial aspects about manufacturing right the first time. But in a reasonable time frame for the number of types of experiments to do to get the drug to the patient, because that's what we're all there for is to bring new NDAs and drugs to patients.

So with that, what are some opportunities for PAT in new development of programs? It really is a process knowledge tool, so we're trying to build the information set for commercialization, looking at all the various variables and capabilities that could be in there from scale, component variation, many of the things that Ajaz already mentioned that experiments are ongoing with. As well as fundamentals with regard to formulation development, formulation solid-state interactions. It gives us a wealth of knowledge about that.

But as we're developing that knowledge, I think that we're a bit cautious about is that it probably really isn't an optimized control tool for clinical development batches. The clinical

development batches will probably provide an opportunity to gain that process and product knowledge, but it's probably not developed to the control tool at that point in time.

As we look forward to putting together the NDAs, what are some potential challenges towards the application of PAT and development programs? Well, comparison is often difficult. We, as we're going through development, batches are often unique experiments for scaling up, developing new pieces of equipment, moving it from site to site. So some of those parameters are changed. We're evaluating the impact on those--on the product that those various aspects and product characteristics, but it's an evolution as we go through development. And, similarly, you know we speak very frequently about PAT in drug products, but there's certainly opportunities in drug substance, but coupled with that synthetic processes are evolving. The route may be the same but, again, we're looking at all the various aspects about changing and scale-up as we go through that.

And in some cases, depending on what the clinical needs are, the size and scope of the program. Experience may be limited. We may not be

making a huge number of batches, really, to look at.

So with that being said about the downsides, I think there are, you know, certainly, some positives. Is that we can look at in development and try to determine what parameters are appropriate for monitoring. We may not determine what all of them are, but it's the beginning part of the look.

As we mentioned, also, the commercial process may be limited at filing. Where certainly at the limits of scale is often in small scale, but we're moving towards the commercial manufacturing sites. But the number and limit of experiences is something we have to deal with. And I guess the one other piece to emphasize, as well, is that very often development processes are very rapidly moving and some of the parameters that I mentioned in the first slide about the challenges, were often material limited. We're trying to serve many different customers in the development program, so we have to be cautious about which ones to serve, but that may limit, perhaps, experiments for how many batches we want to make, say from a commercial or manufacturing perspective because we have to

make sure the clinic stays supplied, as well.

As we look towards, you know, potentially some of the regulatory strategy, what are some of the other challenges towards the application of PAT and new NDAs? In many cases, at least, at this point in time, reference methods are probably still going to be required, whether they be for regulatory surveillance programs by the FDA or other authorities. Compendia monographs, at this point, we don't have a plan for how the USB is going to accommodate that if we have a different product coming off the shelf, because PAT may be relative to the process as well as the product. As well as acceptance testing in global markets. I know this is a U.S. FDA committee, but as a global organization, we look at, you know, certainly worldwide approval of many of our products and many of them will still have certain limits on acceptance testing to bring product into their market. So, you know, we're looking at a global regulatory program and many cases will need acceptance testing for some of those global markets.

I've touched on, already, the size and the scope of the database with which to set criteria.

You know, in many cases, we'll have our best thinking, but what's really a normal process and what's a variation from that normal process versus a true variation and a failure in the process with that limited database is something that's very challenging as we're putting together the NDA.

And the other aspect is, technology evolves over time. As much as we do try to bring forward NDA programs very rapidly, sometimes it is a multiyear process and many of you that are much more deeply entrenched in the technology know, that by the time we actually file an NDA, the technology has moved. So what we start actually looking at with the process in the first couple of clinical batches may not be the best technology tool that we really want to move forward within commercialization. So we have to be cautious of not handcuffing ourselves by looking back towards that early development experience and the tools available at that point in time.

So, as we look forward to that from our perspective, what are some options for some new dossiers? You know, we could just briefly describe PAT that we anticipate doing towards commercialization and just sort of let the agency

know where we think we're going in the future. Or we could go to something more rigorous--change protocols, they've been discussed in various other aspects about filing NDAs and PAT might be a good example of that. We might do things like describe what is the body of data that's going to be needed in the future to move forward full acceptance of PAT?

What changes with the adoption of PAT? Are we going to drop some of the conventional tests? Are we, in fact, going to actually change the manufacturing description? Is PAT going to be an end-point rather than just a control tool that we may do some manufacturing process limits to? And that's just, you know, some illustrative examples of what we may look forward to.

We have to be conscious, as well, if we put a change protocol in. We probably need some description about discontinuing PAT activities. As we go towards commercialization, what if we learn that it may not be the best thing to control, so what will we do if we want to roll-back and relook at something? So any protocol may need to talk about discontinuation of PAT activities or regrouping from a totally different direction.

And, as with anything, like a change protocol, we have to talk about filing mechanisms. Is it going to be, you know, upon commercialization? A supplemental filing at some point thereafter and then we can talk about is it going to be a prior approval? Is it going to be a CBE--a CBE-30, all of those different aspects? Or are we going to be so comfortable in the future, it'll just be an annual report?

So not to be too down, I mean, I've spoken about some of the challenges. But I think that PAT does afford some great opportunities. It does allow us to gather the process knowledge early in commercialization. If we get on-board with what we're going to test, I think, as Ajaz mentioned, the potential for understanding and looking at the process is great with PAT and managed well, it can provide some great input to early commercialization.

With the protocols, it also allows us the opportunity to agree on the dataset being developed so we don't have any second-guessing thereafter. It allows that we make sure we've got the full dataset and we don't have any gaps.

And one of the more challenging aspects

is, will it go to such a level of detail that we'll agree on the criteria for success? And that may, again, come back to what's going to be the mechanism for it? If it's something as straight forward as an annual report type change, we'll definitely need to talk about criteria for success. If it's just going to be the more broad narrative descriptions about what we're going to monitor, that may be something we have to look back at later, and then negotiate on.

And, certainly, as I mentioned, if we have other methods, like reference methods, the protocols, we'll probably certainly need to talk about how we're going to correlate to those reference methods.

So, what are some of the risks? One aspect is that, as we go through and we actually look at it, that the PAT information may suggest that we really, our initial thoughts were really pretty far off the mark and we really have to change things so we have to handle it differently than we originally thought.

The monitoring, as we go into commercialization with PAT may suggest that we see things we didn't appreciate with the early

reference methods. And I know that's certainly an aspect, certainly as we look towards protocols and, perhaps, a bigger aspect as we look towards post-approval type things, like supplements if we move towards that. What do we learn about old products? And I know it's going to be a topic of some discussion, as well.

We're not the only ones sharing risks. I think the FDA, as they look towards things like protocols, especially if we look towards change being affected, supplements or annual reports. They're going to have to accept to a commitment for a future change with a very limited dataset and how comfortable is that going to be?

If we really look towards some of the opportunity being in the post-approval setting, we--maybe we wind up talking that it may be a different area, so we have to think about two different aspects of that: One, post-approval review burden. And the other is: Is this going to be another piece of an NDA in an already very constrained resource environment during NDA reviews. And we have to just be cautious that it doesn't detract from the approval of the NDA and slow down the process.

So, in summary, the opportunities for PAT, you know, they do exist and they're very valuable. At this point, in looking forward, the opportunity may really be in a transition to post-approval activities. Is everything going to be so ready and finalized that it's going to be ready by the time of NDA submission and we'll be able to roll into that? At this point, that's, from our perspective, probably unlikely.

The challenges do exist, both from the FDA's perspective on the need to make the information available so that they can make the right judgments. And, also, from our perspective to make sure that we get new products out there as rapidly as possible.

So, with that, I think the committee certainly has quite a bit to speak to of looking forward to the opportunities in trying to balance the risks and I look forward to hearing the discussion on those topics.

DR. LAYLOFF: Thank you very much, Jeff. I think in our discussions on PAT, many--we've discussed several times where we didn't think the bar should raise and there is a certain acceptance of what a quality standard is for a product. And

that probably will stay with some kind of reference method that we could use in stability in testing or something like that and the PAT--that would be the ultimate reference for it in the PAT. And the PAT would be just targeting that.

Is Steve here? Is Steve here. Okay now we're going to go to Dhiren Shah, from Aventis.

DR. SHAH: Thank you. Good morning, everyone. I'm really pleased to be here to share my thoughts and my company's thoughts on post-approval PAT application and the challenges around it. First of all, I would like to thank Ajaz Hussain and FDA to invite me to come to this meeting and share my thoughts.

As a way of outline, I would like to discuss, first of all, what is the need for post-approval or what I call PA-PAT applications? Is there a need for that, you know? And if there is, you know, how do we address that?

Challenges in PA-PAT applications. Once a product is approved and commercialized what are the challenges in bringing PAT in the regulatory area? PA-PAT applications to APIs, the drug substances, Ajaz spoke about that little bit, and Jeff to the APIs as well as for the drug products. How do we

apply PAT once a product is approved?

Then the real important point from regulatory perspective or a pharmaceutical company point of view, the guidance development, you know, the guidance to the industry that when you apply PAT to an approved product, how do you that work about? CMC review point of view. What do you need from CMC review? Type and amount of CMC information needed? This almost sounds like SUPAC guidances, you know, that's what the workshops and the committees did for SUPAC, that how much CMC information is needed, what type of CMC information will be needed to show equivalents? And regulatory submission type. Jeff spoke about it, you know, the standard, prior approval supplements, all kinds of changes being affected or annual report kind of reporting.

And then on the compliance side, you know, the second part of the equation, which is on the compliance side, which needs to be totally discussed. And then I'll give some summary and concluding remarks?

Why do we need PAT--PA-PAT? Improve quality of existing products. There is no doubt that pharmaceutical industry, in general, is behind

rest of the other industries, later industries--food industries, chemical industries. I've been in this business for 25 years and I still, I know there are products being made with very old technology, simple mixer and stopping the mixer and putting the hand in it to fee the granulation is done or not. Honestly, that's, you know. And, of course there are technologies which are high-shear granulators where you have, you know, kilowatt end-point measurements for granulation being done. But technology-wise, the pharmaceutical industry is backward, it's behind.

And, again, it's by necessity, you know, the nature of our business is such that we stay with that.

Improved analytical testing. Again, we present 80 samples, you my have a batch of 1 million tablets and you may take 100, 200, 500 tablets out of that whole batch and you hope that the samples really represent the whole batch. And that's a big risk thing.

Increase manufacturing efficiencies, again, in some cases you can really improve manufacturing efficiencies by applying PAT.

Reduce, hopefully, eliminate other

specifications, avoid potential recalls and enhance compliance, they all go hand-in-hand. But, by applying PAT if we can really reduce our specification results that will be a big achievement. And, of course, when you add all of those there will be--I am sure that there will be potential long-term cost savings to the companies and ultimately to the patient.

Challenges in PA-PAT applications. There are two kinds of post-approval situations, in my mind. The first kind is products without PAT applications in the original submission, which is majority of the cases, right now, because products have conventional controls where you don't have PAT. Now how do you apply PAT post-approval?

Identify process-critical control parameters. You know, once you identify, then you can think about applying PAT to those critical processing parameters.

Replacement or adjustments to in-process controls and, possibly, final specifications. Once you find out that certain PAT can be applied, for example, for blend uniformity, or for tablet hardness, how do you take the conventional, in-process specification and then apply PAT to

that? And how do you replace that? And that's a challenge.

Correlation between PAT-based controls and approved conventional controls. This is very obvious that you already have products with conventional controls in place, how do you correlate that with the PAT control?

And of course, the review and compliance issue. This you will hear time and time again, at the end of the day, you know, our products are approved and when you make changes without the review processes, without the compliances processes that will be used to allow us to change to PAT.

OOS--out of specification--that will happen, you know, that has always happened, with the best intentions--with the best products, out of specifications occur, how do we handle that?

And, in my opinion, for products which do not have PAT, it may be difficult--not impossible--difficult to apply PAT post-approval.

The second scenario is, obviously, for products where you already have PAT, that is, again, looking in the future. You know, right now as we understand, there are not too many prods with PAT in place for manufacturing the commercial

products. For these type of products, changes to approve PAT-based controls, Jeff talked about it a little bit. That once you have some PAT controls in the initial phase, but then you learn, with time, that maybe you don't need that or you want to replace it. So you may want to change the PAT-based controls after approval. Addition, you know, you may realize or you may understand the process more and you may want to add a new PAT-based control for a given product.

Deletion of a specification to eliminate non-value-added controls. In the, again, with a limited experience, going into NDA, you my have some in-process controls, but as you learn that some of those are, say, for example, non-valuated, how do we replace those or eliminate those?

Again the review and compliance process, that needs to be defined. Same old question, out of specification, how to handle it? And I believe, in my opinion, it will be much easier for products which already have PAT in place to make post-approval changes.

For the APIs, very quickly, how do you apply PAT post-approval to APIs? The first, is there is no change to drug substance pathway, it

remains the same. And then in-process controls, such as impurity levels, at different stages of synthesis, maybe you want to monitor using PAT. Residual solvents, including, moisture. Examples, could be completion of reaction, whether the reaction is completed at a given stage or not.

Isolation purification steps; initialization and completion of crystallization at the very final stage.

So, those type of things can be applied, those are the examples which most of us know for in-process controls for the APIs.

Correlation between the conventional IPCs, in-process controls, and PAT-based in-process controls. Again, we need to have some sort of correlation. And once you have PAT-based in-process control continuous monitoring, how do we handle API specification? And what will be the role of the final specification for drug substance?

And we all know the question about parametric release, which started out in sterilization area, but can we apply parametric releases after we have certain appropriate PATs in place for the APIs?

Post-approval PAT applications to drug

products. Again, there is, I'm--there is no change in drug product components, composition, and basic manufacturing process.

Drug product--maybe we can consider drug product type dependent PAT applications; solid oral dosage form, both immediate release and modified release; sterile products, semisolids, so we can consider based on the noted form dependent application of PAT.

Raw material controls, ID, assay uniformity, some critical physical parameters, like particle size of an excipient. If it is critical for the product, you know, can you apply PAT?

In-process controls for drug products, for example, granulation end-point, most of us are familiar with that. Moisture content in the granulation; blend uniformity, content uniformity of the dosage form. In case of semisolids, maybe, viscosity measurements.

So those are the examples, and I believe the correlation between the conventional in-process controls and PAT-based IPCs will be very important, as we move forward with this concept. And, again, when can we and how can we use parametric release for dosage forms when we apply PAT?

Guidance development for PA-PAT-based controls from CMC review point of view, we need to establish equivalents to conventional controls. How do we establish to a comparative protocol in an NDA or post-approval, how do we do that? And that's where we need, I believe, some sort of SUPAC-type guidance as we move forward with this technology.

Enhanced assurance that the product will meet what I call SIPPQ-strength identity, purity, potency and quality? How to show those, how to establish SIPPQ.

Scientific basis for PAT controls, we are to justify the PAT controls. And then, obviously, as I said earlier, the type and amount of CMC information required, you know, how many batches you need, is 10 batches sufficient; 5 batches sufficient to apply or make this change post-approval? And the scale of the batches. Does it have to be at commercial scale or pilot scale, of lab scale?

Statistical support--what kind of statistics will be required to support such a change.

Stability requirements, is there any value

of doing some stability requirement when you make this type of change from conventional in-process controls to PAT-based?

Post-approval commitments--any post-approval commitments, like, long-term monitoring of the process, in forming more data, you know, after the change is approved?

And the regulatory submission type, Jeff talked about. Could it be--can you do it through annual reports? Are changes being effected in zero days or 30 days or prior-approval supplements?

On the--I should back off for a second. Okay, I'll--before I go to summary and conclusion, I have a slide to show on the compliance side the industry will be looking from the agency that when you make post-approval changes, going from conventional in-process controls to PAT-based, how is the auditing system will work? The compliance audits of the sites? Is the change done appropriately? What kind of things will be checked? What kind of statistical data will be checked? So, those types of guidances we'll need on the compliance side.

On the summary and conclusion: In my opinion, PA-PAT application is easier for original

application with PAT, it's very obvious. But when you go from a product with no PA-PAT, it will be more difficult to apply.

As I said earlier, difficult for original application with conventional controls, it's very obvious.

Proof of equivalence and enhancements--industry will have to show and agency will have to accept that when do you show or how do you show the equivalence between what you have and what you will be changing to?

Validation, you know, proof is in the validation. When you make a change like this, how do you validate, you know, what kind of validation protocols will be required?

How to deal with out of specifications? Rule of compliance, that's very critical for this type of activity to go forward. And incentive for the industry, cost benefit. As Jeff said, industry is under tremendous pressure to bring new products fast and, again, we always analyze, what is the cost and benefit. If we change post-approval to PAT, what's the benefit to the company? Can we reduce, you know, our OOSs? That will be a big benefit for us. From compliance side, if you can

make it easier, that will be a big benefit for us.

And then training of industry as well as FDA staff, that's very important, our training on both sides of the equation as we move forward with this. And I welcome FDA's--this important initiative, which is, as I said, you know, the industry is really behind in the technology, when it comes--when you compare with food industry or other industries. And I think this type of technology is badly needed. Thank you.

DR. LAYLOFF: Thank you very much, Dhiren for bringing us more about the complexity of it. I think FDA's going to have it's job cut out for it. And now we'll--

DR. MILLER: I'd like to make a comment.

DR. LAYLOFF: Okay, sure.

DR. MILLER: And I appreciate very much your discussion and coming to your summary. We have heard through external organizations, such as CAMP and other external comments about the care and sensitivity of just focusing on making the guidance and the regulations simple and easy for original PATs. The concern, from these organizations and other discussions are of current product processes in place, to have sensors applied to them and

technologies applied to them will require more efforts by vendor companies. If we go down a pathway of just selecting easy regulations or very open and general regulations for original PATs, vendor companies feel that there will not be enough activity or action for them to stimulate their companies to advance technologies to meet current needs and future needs and I--Eva's nodding her head across the way. I just want to bring that to the forum here. Please be very careful about how we give the guidance or how we make the guidance for the future.

If it is so very narrow, we will not have the external technological industries wanting to be partnering, it will be too small a business. And they will not want to waste their resources or time. Just need to get that on the record. Thank you.

DR. LAYLOFF: Yeah, it has to be a win/win for the vendors, too. I mean, if it's not win/win for the vendors, it's not going to work out either. Any other comments before we go on?

[No response.]

DR. LAYLOFF: Okay, going on to Hank Avallone, another FDA alumni--alumnus.

[Brief pause.]

MR. AVALLONE: While that's happening, I just wanted to sort of share with the committee the parts--at the first meeting, we had discussion that the subcommittee and the working groups are essentially more technical and focused individuals and the regulatory affairs seem to have been missing in that discussion and that was the reason I invited Jeff and others to sort of give that perspective so that the committee understands the challenges and so that we can craft a way forward addressing those challenges.

DR. LAYLOFF: I think that, earlier, looking just at technologies doesn't really address how it's going to fit into the win/win situation and even bringing in the vendors, it has to come there also. Are we ready now.

MR. AVALLONE: Yeah, I think we're ready to go, Tom. Thanks. I just want to start it out by thanking the subcommittee for inviting me here to make this little presentation.

It's to--just to give you some of my background--it's--I was in FDA for 28 years as an investigator. I looked at day-to-day problems for 28 years. I went with Johnson for the last seven

years and I kind of picked up that same role. I looked at--now I don't look at day-to-day problems, I look at day-to-day opportunities.

What--some of the issues that--and this presentation is given from an operational compliance perspective. And it's a little different--maybe a little different slant on PAT and how it's going to affect our operations from an operational perspective and from a compliance perspective.

I date myself with this first comment and I think I started--well, I started in the industry in 1965, late 1965 when the GMP regulations were first--started to first evolve. And the comment that I recall that stood out that Ted Byers gave and that a number of PMA company quality managers always gave was that it's important to design quality into the product. We need good development in order to have a quality product.

And I think that has--that's the one thing that I think has stayed with us over the time. In the last 10 years or so, FDA has become more involved in this in looking at the development aspect of our products with the pre-approval inspection program. And I think we've all--have

more of an awareness of the need for good development.

And just, since I have this floor here for a couple of minutes, I just had a couple general comments that I've heard some of the other speakers present.

One of the issues that I think we all have to understand is that the biggest--the major compliance issue is old products at today's standards. The bar is constantly being raised. It's not going to stay, it's not going to stay where it's at. Day to day it's going to move up. From an industry perspective, this offers me some type of competitive advantage over other companies so I'm going to look at it from that aspect, also. I think we need to recognize that PAT is just one part, one of the drivers for improved product.

There are a number of drivers for a quality product and when we look at this and it's something that our development managers need to be aware of and I constantly remind them of this on a daily basis when I look at the old products and I look at these opportunities as they arise in my company.

The first one is really operational

environmental exposure. We're getting more and more pressure to have concern for the operators, to minimize--so that they'll have minimal exposure, minimum toxicity coming from the products which they work with on a day-to-day basis. When I develop a product and I have to look at this and look at manufacturing processes and systems and procedures that will give me this minimal exposure of operators.

Another area that we look at, another driver, would be the manufacturing technology and this is improving all the time as equipment is evolving, new, better equipment's evolving, better testing is evolving. We should look at raw materials. And many of the raw materials that we use are purchased as open materials, have fair-trade raw materials. And I think it's important for us to develop specifications that are tight enough that will give us the consistency and standardization for process. And we'll talk about this in a few minutes. Also, the API, it's critical to look at this aspect of it, in terms of the physical form of it and standardize and control that.

And I mentioned equipment, really we're

looking at equipment that's closed and that's cleanable. I have to turn around equipment that, from an operating company's perspective in a short period of time. I have to be able to gear up from one product to another. So some of the large, process trains clumsy equipment that I have, I think I'm going to have to take a look at when I develop products.

Basically, I've given the charge and I had a meeting the other day with the VP of R&D. And my charge has been, since I came to Johnson, I want direct compression products, I don't want any wet processes, I want to keep it simple and that's the theme you're going to see with this presentation.

Operating costs, again, minimal steps, keep it basic. That's going to give me the benefit in terms of day-to-day operation. I mentioned the cleanability of the equipment. My cycle times are going to be reduced. I'm going to have to turn the product over, turn this equipment over as many times as I can.

Improvements in analytical technology and we're talking about here at this forum PAT, but this is coming through as just one of the improvements in analytical technology. I'm finding

more about my existing products and, certainly, when I come up with a new product, I'm going to have to look at it a little closer because I know this product is going to have to withstand increased scrutiny over a period of time.

I'm going to see flaws in my existing processes, products and I see them. And I see them they come out in stability testing. I see them on a day-to-day basis.

And the other piece here that we have to look at in development is nonconformances and documentation review. Again, the more basic the process, the simpler the process, the less opportunities I'm going to have for nonconformances, the less opportunity an operator's going to have to do something wrong and the list of mistake I've going to have, so it's going to improve my compliance level by having a product that's developed to a standard--to today's standard.

Certainly, when we talk about compliance issues that my real concerns are dose uniformity, dissolution, and impurities. I think PAT is moving forward, it's going to address the dose uniformity issue relatively well and the impurity piece will

tie along with that. The more difficult piece is the dissolution piece and this is release-rate piece. And I think this is the aspect that we're going to talk about when we get into raw materials and why it's important to have a simple process, few raw materials and that I have control of the distribution of these raw materials.

With regard to the API. The physical form is important and it's important for the developer of the API to communicate with the developer of the dosage form. Two days ago, again, I met with the R&D person and he commented that we have a new product coming down the line and that the API developer has given him four different physical forms of the API for him to work with in developing a directly compressible product. And this is necessary to go that way. I think the days of taking a raw material--I get what I get out of the crystallization process and I just mill the hell out of it and I get a nice micronized particle or reduced particle size and I can go ahead and manufacture. I think those days are coming to a--I think they're coming to an end when we start looking at formulation development.

From a GMP, a validation perspective, this

probably--the physical form of the API, prior to milling, probably gives me the best indicator of the control and the consistency I have in the manufacturing process for the API. So, I want to establish a specification--a meaningful specification for this material at that particular stage and I may even be able to get by without a micronization process or an extensive milling process of the API I'm manufacturing if I'm able to put more control into that aspect of it.

With regard to excipients, again, I want to keep the number short, I want--I want physical aspects monitored, good specifications for these physical aspects of the excipients. And one of the concerns that I have now when I develop a product is the excipient uniformity. It's not just the active uniformity, but I want to know, for example, what's the distribution of my stearate in this particular product? I think another presenter commented on that excipient and it certainly does have a major effect, kind of a major effect on my release rate. So I want to make sure that I have a process that gives me the right uniformity of that and the right characterization, particle size and control of the excipient and the API.

From an operations perspective, I'd like to have multiple sources and one grade of excipient. I know our developing managers sometime like to get somewhat novel and go to a single-source excipient that may be in some, you know, location that's maybe out of the United States and this does present problems from an operating company's perspective. Again, I want to keep the excipients relatively common ones that probably have multiple sources on them.

The ideal process, from my perspective, is the direct compression process screen, blend, and compress. And this enables me to have a closed system. Toad system--I can weigh, bled and load the press directly from a container. When we look at some of the existing systems and I know when one of the--I guess one of the issues that I was concerned about when I first came to Johnson was, in J&J we have a lot of fluid bed processes and in my travels throughout the industry and in the New Jersey, Philadelphia, New York area, I never really saw much of fluid bed processes and I think probably because of the competition but, also, because of the recognition that when I look at a fluid bed process, I'm looking at a very complex

process. And from a compliance end, this, again, presents a lot of opportunities for me to have nonconformances.

Going back, I guess historically in days of training FDA investigators, one of the things you point out is when you see a piece of equipment and you see a lot of dials on it, you ask the company, what do all these dials do, what kind of controls do they have around them? And now with increased computerization, we start getting more printouts of alarms, alerts, things like that and so I want to cut these--this number down and this complex--relatively complex equipment is going to increase my process time.

I recognize there may be some processes that this is needed for but, again, when I look at when I look at development today, my first choice is direct compression, simple processes and, again, that ties with PAT, with the analytical aspect of it from a dissolution and a constant uniformity perspective.

In discussing cleanable closed systems, we're looking at wash-in-place tablet presses, also, where, again, I have the minimal operator exposure. I have the good cycle time, I can turn

it over relatively efficiently so I can move forward in that area.

As I point out, PAT, along with any other analytical--new analytical technology is going to identify flaws in my process if the process is not properly developed. So I think the--one of the messages that I've taken away with PAT is I have to have a well-defined, a well developed process that's consistent, otherwise PAT is going to show me the flaws in my process.

And this is another comment on the direct compression piece of it. Again, less variables, less steps, less opportunities for nonconformances and that's where I'm looking at it from a compliance aspect.

One of the concerns in cycle time in manufacturing is the documentation review. I can move forward PAT and improve my cycle time, my processing times, not stop the process, but what stops the process is, really the documentation piece, the review of records, the nonconformances, the problems that occur in the manufacturing process. So, if I move forward with that I think I can tie in with PAT and have the process that's properly developed that's going to be consistent

and from an operational perspective, that I'm going to be satisfied with.

In--just to wrap this up, in conclusion I've talked about the development from an operational and compliance end and hopefully this ties in with what you're addressing in your areas of PAT. Thank you.

DR. LAYLOFF: Thank you. Any questions for Hank, comments? One comment, Hank, I've hung around this business for probably about as long as you have and I think the bar for solid-dosage forms hasn't changed much, content uniformity's pretty much the same over the period of time, dissolution, after we once put it in place, has been pretty constant over time. But what has changed, I think, is excipients in APIs. I'm reminded that I was looking into sucrose one time because I was fascinated with the proposed change in a monograph, and I contacted one of the guys over at food chemical codex to find that they had changed the lead limit on sucrose. And I said, was that because of some eminent health hazard associated with using sucrose and tablets that didn't occur in soda pop? And he said, no, it was technically feasible.

And it seem like, in the case of raising the bar that the bar has been raising up on excipients and APIs to what is technologically feasible, but since our statistical sampling is absurd, we've let the other bars stay about the same. Anyhow, thank you, very much.

DR. MORRIS: Tom, could I ask a question of Hank?

DR. LAYLOFF: Sure.

DR. MORRIS: Hank, I wanted to clarify, you made the comment that you must have a well-defined controlled process or PAT will show flaws, is that?

MR. AVALLONE: Yes, I think it--yes, I think when you look at large numbers of tablets, you're going to see issues if the process isn't well developed and uniform and consistent and we see that then in the--one thing I didn't mention, you know, with the analytical technology to kind of give Tom a plug. If Tom was probably in the St. Louis laboratory right now, you'd have--you'd probably have your products tested using this technology right now. Is that a fair statement, Tom? Right. So, I think that in looking at this technology, as we move forward, we're going to find

problems with processes and I've seen it with some of my products, now--I'll give you an example.

I looked at some of my annual reports for a product over a year's period of time. And I look at my content uniformity of this product. And it ranges from about 96 to 104, real good, tight content uniformity. But every now and then, I get a 62, right. I'm looking at this thing. And the question is, right now, you know, and now Joe gives me one or two a year that I can retest. I get one or two of these. And when I look at this, I have to take a step back and say, is this a real number or is this just analytical error. And it's a difficult call to make right now. But, again, if I look at over a year's period of time and I'll look at 40 batches. And I'll have one batch that comes in or two batches that come in with a 62 out of it.

All right, I think if you looked at PAT for this product over--with--for individual batches, if you looked at 10,000 tablets, you've really done or looked at--or even more--you're going to find, possibly, one or two of these tablets in that batch. And with the testing that I do now is destructive, so it becomes a little bit more difficult question, is it analytical or not?

But with this technology, you're going to have that tablet, you're not going to destroy it. And you're going to know is it a real number or not and you're going to have to deal with it. And I think that the issue is going to be, if you don't have the good manufacturing, the consistent manufacturing process, you're going to have problems in this area.

You're going to find things out that you didn't want to know you had--you knew.

MR. COOLEY: Could I throw out as maybe a challenge to the group, that by using PAT, it may be a way of getting to better process control and better process understand rather than meaning that we have to have better defined processes to make sure PAT never shows up a flaw?

MR. AVALLONE: Well, I think they work--and that's maybe I didn't get that point across, but I think you really need the--you need the two, I mean, you--I can't just say I'm going to go to PAT if I don't have a process that's really--that's well developed and it's consistent and it's uniform.

MR. COOLEY: But couldn't PAT get you to that if you use PAT in the development stage, don't

you feel you could get to that stage much faster by having more data?

MR. AVALLONE: As Jeff pointed out, I think where you're getting to is--I don't know that--as the process moves along--it's moving along pretty quick and I think you're probably going to--PAT is probably going to come in once you get into the operational stage rather than in a development stage.

I gave you the example, that I have a product now that's going now into probably phase three, and my API supplier, research guys in API gave me four forms of it. And we're looking at different--at three or four excipients to manufacture a direct compressible product. So, I want to get, if I get--put everything together and I get a product that's consistent, that's well defined, and well developed, when I put this in my operating plant, then I'll be able to utilize PAT, it'd be a good--it's going to be a good candidate, hopefully for PAT technology. Not at the development stage, though, I think it's too early in that stage because I'm still working with the product and I'm going into, you know, I'm going into trials with this particular product, so I need

to define it now and maybe at a later point in time kick in the PAT.

DR. MORRIS: Tom, could I raise a point as well? Two things, one, Hank, is that you may find flaws in your process that that's of course the case, but I think part of the charge of the committee and part of the reason that we're all here is that if we find flaws in a process that's one thing, we don't want to find flaws in the process that are really because the sensors haven't been properly applied. And that's sort of more of this, I hate to say safe harbor, but that's sort of more of the concept of saying, during the period when you are applying them that you don't artifactually develop data that makes it look like there are flaws that really are just a function of the fact that the implementation isn't really done, just as a point of clarification.

The other point is that with respect to development batches, we've pretty well, I don't know how many batches of things we've run over the years, but the idea that we've embraced as much as possible is actually another one that comes from Father Tom here, which is that PCCPs are what are important. The value may change, as you scale, the

value may change as you change process conditions, but if you truly have identified a critical point that needs to be monitored, the fact that that's the variable that needs to be monitored doesn't change. The absolute value may change, so thereby, I would say there's significant advantage to doing it during process development, during clinical manufacturing, all along the way. Again, once we're--we'll have to think of a better term, but once we're through the point of making sure that we properly applied the technology.

MR. WALTERS: I just had a comment. I feel that if you apply PAT to any properly developed process today, you will find some variability which may not necessarily mean flaws in your process or your product.

MR. AVALLONE: I don't know that, again, I gave you the example, I don't know that I would agree with that. By today's standard, if I have a well-defined process that's very consistent that gives me good reproducibility, then probably it is a--it could be a candidate for PAT. I think that the issue that's going to come up, I think that I'm struggling with is the release rate in the dissolution piece of it.

I think the technology is probably moving there and I'm not, maybe, the expert on this, but I think from an activity perspective--a dose uniformity perspective, I think we're getting there, but I think the other piece to demonstrate the uniformity of the excipient in the product is maybe not there. I think that's the tougher--the tougher issue that PAT is going to have to, you know, to deal with is the release rate and dissolution. And that's why I'm looking at--the ideal candidate would be a directly compressible product, few excipients, few variability, uniformity of the excipient so I can control that aspect of it with technology.

DR. LAYLOFF: One of the things we've been talking--we discussed previously was that most of our process stream has been monitored through the API all along and the excipients have sort of been ignored. They've just sort of been hung along with it, which, of course give you the problem and if you start looking at dissolution properties, because you're not monitoring the whole--all of the materials in the blend, you're just looking a that a single component of it, which gives you a warped view of things.

The other think I'd say on an outlier--you have a nice population if you find one out there. When you have analysts in the laboratory doing routine analysis that--and you're doing it destructively, it's very frustrating. I mean, I had an analyst go back and run a tablet--a bottle of 1,000 to try and find another 50 percent tablet. And it was probably the analyst error that cost me two or three weeks of your tax money.

MR. HALE: Okay, I think that there's been a lot of talk about using PAT to look at existing products with existing processes as opposed--I think where our real opportunity is is to use the testing capabilities to design processes that are inherently scalable, that are inherently measurable, and that are inherently controllable, which does not always exist with current technology. So I think if we limit ourselves to thinking in terms of how we measure things with the existing scope, we will be limiting this whole process. Where the big gains are, I believe, is not measuring more things but allowing the measurement to allow better design and it has to go back into development to get the optimum advantage to this process. If we limit ourselves to batch

processes, if we limit ourselves to specifications that were built around old existing products and processes that we will not allow ourselves to create the advantage that we could here. And that it has to be in development where--and the development of these products and processes that meet the new criteria and not constraining ourselves to the way we've done it in the past that's the static blending systems, the granulation and all of these things don't necessarily apply anymore and we need to be able to do things that we haven't done in the past.

DR. LAYLOFF: Art.

DR. KIBBE: I think, Tom, hit on a good point. I was going to try to get there, but I'll skip that one and go to my next point. We have had, during the evolution of pharmaceutical manufacturing continually improved our ability to analyze what we do. And this is one more step and it's not anymore frightening than any other step we've taken.

Remember when we couldn't measure penicillin down to the amounts that we can now and we've added a whole bunch of process to make sure there's no penicillin contamination. Well we would

have never have done that if we couldn't measure penicillin to our levels.

And the invention of pharmacokinetics was because we actually started to be able to measure the drug in the blood supply so we could actually make some measurements. So this is no more, I don't know, it's an evolutionary process, not a revolutionary process. And if we take that in mind and we say to ourselves, what are the standards that we need to have to assure safety and efficacy in the patient and if we can monitor 100 times better than that, that doesn't mean we need to change our standards. And I think companies don't need to be afraid of the fact that we're going to look for a 5 percent variation from a tool now that measures 1-1-millionth of a power variation that we had before.

I think Tom's right. This is an opportunity for the industry to come up with way of improving the process so they can save time, save money, reduce batch failures and out of specifications. And know when the process is starting to go, long before it gets out of the specs it's needed to get it approved for use in humans, so they can make those changes in those

things.

Tom also said about the odd numbers from analytical. Well, if you have a nondestructive method--the nondestructive method can be validated against a destructive method, you can go back and look at it again.

I mean, I look forward to the day when every tablet that comes out of the line has been scanned and we get a uniformity indicator, maybe a fingerprinting, as we talked about before, that gives you a sense that there is, indeed, the right mixture of all the excipients and the active in it and you can see during the run that this moves slightly. But it moves within a constrained environment, because the run is not absolutely perfect. But we accept that because we know that the variation in it is not significant clinically in the end line as the clinical variation.

So, I think if we can assist the FDA in writing guidelines that makes that clear. And the industry looks at it as an opportunity to save money, to have a better control process, to be more sure of their product that they make, I think it's going to be, you know--work out well. And I think we can do that.

Now, one of the things that we're doing today is focusing on solid-dosage forms. It might be useful for us, I think in the long run to focus on that as we develop the guidance and then allow it to expand to things other than the oral solid-doses form, which seem to me a priori to be a little bit easier to handle in most cases.

DR. SHEK: Tom, I want to just re-emphasize what the thing Tom was talking about and what, Frank, you had--Frank, you had in the first light, okay. Talking about building in quality into the product.

I think we have to look, PAT is another analytical tool and PAT wouldn't make the product better, it maybe become more efficient, you know, the way to test it--a better test, but opportunity, I absolutely agree and I was a little bit disheartened to hear that you know, Ajaz, from you, evaluations within the industry are, indeed, people are a little bit reluctant to look at that. I think that's a great opportunity there basically to build the quality into the product understanding the process.

And I would like to push it further, it can be also product--existing product that a

company decided they'd like to improve the process. I think here there is an opportunity to use PAT and maybe with collaboration with the regulatory agency to facilitate this change, because here we'll have data where we can really use--and I think that's--that's where, really is the game--we can this way to improve the quality of the product that we have today and make it more efficient and effective.

DR. SHAH: Just a comment on what Hank said. I my experience, less than 10 percent of solid oral dosage forms are manufactured by direct compression. You know, most of the products are manufactured by the conventional wet granulation process. The dose may be too high, the solubility may be too low, whatever the reason, but the majority of the products end up going through wet granulation process.

Dr. BOEHLERT: I just wanted to make one other comment. We've been talking about using PAT and learning things about your process you wish you didn't know. But, in fact, some of those concerns are happening today as manufacturers go back and look at old products with new technologies.

My experience relates most often to the

laboratory kinds of issues and if you look at an old product with a new method, you may, indeed, find things that you didn't know. It may, indeed, not meet the requirements that you have on file, but in the end, what's going to be important is whether there's any impact on safety or efficacy of that product. The product itself may not have changed. It may have always been the way it is now. What has changed is the way that you look at it and we need to keep things in perspective, you know, have safety and efficacy been impacted, or do you just know more now about the product that's always been out there?

MR. HUSSAIN: Tom, sort of two comments. One is, I think with respect to a lot of the regulatory risks that you want to deal with. I mean, we have posed for you a set of questions, if you could sort of go through those questions, I think this discussion really fits in very well with that. And that's the reason I asked you to sort of move the training discussion to the afternoon.

But the point I want to make is in the sense, I think we all believe that, you know, we have to build the best product and so forth. An my concern, I think, just listening to the discussion

here is the pressures on R&D seems to be quite significant to just, you know, move forward. And my concern is in the sense in many ways if proper care is not taken you actually risk losing your clinical database itself. Because the products that you use for clinical testing really have to be good quality, too.

And so the trends have been in the sense to go with delaying formulation development as late as possible because of the high failure rate in clinic. And that's the reason I said the manufacturing problems that we see--yes, many old products do experience that but more and more the newer products are having manufacturing difficulties, too.

So I think the reluctance, and Efraim pointed out in a sense, what I have heard from many people in R&D side is, in a sense, we don't have the time to deal with this, so don't sort of bother with it. And so I think how will we turn that around, I think is through time and through education and so forth, because a lot of the formulation development activities an the people who do that may not be aware of these technologies and how it can help them develop a better product.

So, with time that will come around.

DR. LAYLOFF: A couple more comments. I think with respect to time, I think at some point we will see a formulation driven in part by the technologies that you're using to assess it. That you might have surrogates to assess product quality. So you actually look into the product design by the technologies you're going to assess it with.

But I don't think that PAT is going to bring to the industry, the revolution that came when we went from spectrophotometric methods to chromatographic methods. I mean, you talk about opening Pandora's Box, that did it big time. I don't think the current path on process control will impact what we do as much as chromatographic procedures did.

I think with that--oh--

DR. MILLER: So, Tom, just to concur and substantiate Ajaz's last point, I gave a presentation to the Philadelphia Pharmaceutical Forum on May 9 to about 75 people about PAT and all of our activities, past and present. And probably there were 60 formulators and developers from more than a dozen companies and this was absolutely new

to them. PAT is new to formulation and development personnel in general. They have caught a couple buzzwords through, you know, with they have read or heard, but it, in general, in May of 2002 in the Philadelphia area to a dozen firms, the sense is--my senses were that this was new and they have not had the opportunity in the past to use sensor technology in the formulation area.

I'm not speaking to chem development people where APIs are routinely monitored by sensor technology, but formulation developers, it was very clear that this is new terminology, new thinking and they will have to be trained up and deal with it.

DR. KOCH: Tom, if I could make a comment that's relative to things going on in other industries, the last 10 years has evolved from what was an analytical profile, in terms of acceptance of raw materials and final products to often a performance-based forum for deciding on whether to accept products, et cetera.

So in many industries, things have been changing. The use of PAT in those industries has change the way analytical is being done, often much more predictive and inferential analysis is showing

up. So I think the type of things that we're seeing here, in terms of a trend are consistent with what's been happening in other places and will only be of a benefit, long term, to this industry.

DR. HUSSAIN: Tom, sort of a request, in a sense if you could consider sort of structuring the next part of the discussion on the questions that were posed and go through that for the rest of the--

DR. LAYLOFF: After the break.

DR. HUSSAIN: Okay.

DR. LAYLOFF: Before we take a--we're going to take a break very shortly, but before I do, I wanted to point out to you that the Process Analytical Technology initiative has been posted on the dockets for your comments. So if you go to docket--go to www.fda.gov/dockets to number 02D-0257. That was recently posted up, again, it's www.fda.gov/dockets and it's number 02D-0257.

And with that, it's in the back of the handout on all your handouts at the table. And with that we'll take a break for 15 minutes.

[Morning Break.]

DR. LAYLOFF: Okay, attached in your handout is a series of questions, which have been

posed to us by the FDA. And I'd like to have us address those at this time. Ajaz, would you like to go over the--read the questions?

DR. HUSSAIN: I hoped you would that.

DR. LAYLOFF: Okay, I'll read the questions.

Question one, that's a good beginning--question 1: How would the committee articulate its shared vision of pharmaceutical manufacturing and CQC/A using PAT? Hasn't been met with enthusiasm.

MR. COOLEY: Tom, one question I have on that is maybe Ajaz could kind of expand on what you were looking for on that? It wasn't real clear to me what you were asking for--is it a mechanism, you know, going out on a road show or exactly what did you mean by that?

DR. HUSSAIN: Well, let me, maybe I should go back and--one of the aspects, I think, which we think is important is to clearly define what we mean by PAT in the sense--from a regulatory perspective as we start developing a guidance and so forth, and essentially what I've asked is ensuring a proper definition of PAT is important for the purpose of developing regulatory policies

and procedures. The definition would need to be sort of sufficiently broad to help the public and industry realize the benefits of the shared vision of PAT, yet be specific to draw distinction between the PAT concept of continuous quality control or assurance and the current approach that emphasizes lab-based testing to document quality. In a sense, what does the--what I was hoping to get some sort of dialogue from the committee is how the committee articulates its vision for pharmaceutical manufacturing and the continuous quality assurance paradigm under PAT.

In a sense, are we on the same page in terms of PAT being a tool to understand your processes to a degree that essentially says end product testing is either unnecessary or minimal or what and that sort of a thing. Because once we use that, sort of discussion, then we could actually want to discuss the difference between the traditional parametric release and the PAT-based continuous quality assurance and should we draw that distinction or not. I want some discussion on that topic.

DR. MORRIS: Can I, just--one point that might be worth considering is that there's really

sort of two ways of applying this, I mean, in general, and all in-between. But one is that you follow a process and monitor its progress and if it starts to vary, then you know it's varied and you have, maybe, an assignable cause or something to look back on.

The other is that you use the feedback from whatever technologies you're using to control the process, which is quite a different set of circumstances. So I don't know if that needs to be encompassed in the overall articulation. But, certainly, something as a subcommittee we need to address. And, certainly, in terms of what it would mean in terms of shifting mentalities for the regulatory side.

MR. HALE: I think to expand on that--there are not only control of the process but there are the ways of communicating between industry and FTAs in the specifications and how are you going to release product and that seems to be the fear here. But, as this--as the processes develop, there are multiple ways to release product, whether it's by testing physical product, properties of set sample, or releasing based on immediate measurement of a particular dosage forms,

those specifications will be different. So that needs to be added, I think, to this, too.

MR. CHISHOLM: Yeah, I think , that I could try and give you very briefly a summary of what the AstraZeneca vision for want of a better word is. And I think, for new products, which is where we're focusing from now on, it starts, actually, in formulation design and it needs to go that far back. That doesn't mean that you can't apply this to existing products, you can, quite successfully. But if companies are going to look far ahead, then their own executive directors have to get this accepted both by the pharmaceutical side of things as well as the operational side of things. And that's where you get the true benefit.

So, firstly, it's about formulation design. Secondly, it's then, having got that design, it's about technology transfer, because it helps you with that technology transfer. And I think that's why the last time you used the word--let's include the word continuous, as well as batch processes to enable the technology transfer in a much easier way.

It then has come down, next, after that in your manufacturing process to real-time,

statistically-based quality monitoring. What you're actually doing is statistical process control. And if you think of the thing we're thinking about, which is a tableting process, that's right up to and including blending before you go into the tablet press.

Once you get into the tablet press, there's not a lot you can do if you haven't got the previous batch right. What you have to then, for our friends in regulatory, of course, is to do the old-time quality assurance. So you statistically monitor tablets--statistically based, like all other process industries across a batch.

So, I think that's the vision we have of the starts, basically in original design and goes all the way through to real-time quality assurance. I think that's what the FDA is really thinking about with the term they're now using, the term parametric release, I think's totally unsuitable for this because it's about process and product, not just about process and I think the thought about parametric release in the past has always been more about process. So that's where I would be coming from on it.

Dr. RUDD: Yeah, it's interesting, I

think, we starting to get a bit of clarity on the, let's say the differences or the difference in priority which seems to exist at the various stages of development and manufacture where PATs can be used.

I think in terms of any definition and terminology, what we have to get clear, we've said all along--the quality-by-design concept is what we're interested in. I think it, therefore, is crucial that we think about PATs first and foremost as a development aid--the process understanding, the process signature, the process characterization comes from the use of PATs in development. That will be limited, for reasons we've heard already--aggressive time scales; lack of materials; lack of variation in materials; all of these are constraints in development. But you can get so far.

You can begin to build a picture; build a model, start to get some understanding of the process. At that point, you then have the transferability of whatever technology you've developed at that stage and you continue to refine the model. You need to use larger-scale information, greater batch numbers,

manufacturing-based information to refine the model that you've developed in the development phase.

And the PATs will be used there, but differently, subtly differently from how you've used them in development.

And you then get onto the--what you might call the routine use of PATs, where the process understanding bit is almost gone, you know, it's too late to worry about that. And I think what then ensues, as Bob and one or two others have said, you're then into the use of PATs as an enhanced form of statistical process control. If the process is in control, if it isn't varying at all, that's fine. But if there is subtle variation and if there's gross variation, the PATs can help you bring it all back in again, the feedback approach that Ken has talked about.

So what you've got there is, although the enabling tools are maybe the same all the way through, you've got different prioritization, different drivers, depending on which part of the business you're in. And the definition and the terminology will need to reflect that. We're not talking about a single label PAT that applies to all of those situations.

DR. HUSSAIN: That helps in a sense because David had presented sort of his vision at the first meeting and so did Bob. And Pfizer had its presentation of their vision of PAT and it was just sort of very similar, right at the first time and so forth. So I think what David just sort of outlined as the hierarchical aspects of PAT in different uses, I think. So that's what the definition and the use of the term should truly reflect.

DR. LAYLOFF: Okay, we are going to question number 2: Define CQC/A. Should CQC/A be distinguished from parametric release?

DR. HUSSAIN: The whole concept, I was struggling with the term because I think the camp folks have used CQV and they put a trademark on it, so I said I can't use that term so--[laughs]

DR. MORRIS: I'm sure they'll license it to you.

DR. HUSSAIN: So, I didn't want to use that but the whole concept there simply meaning that you're controlling your processes, the feedback and what not, so that at the end of the production cycle essentially you're done, you don't have to wait for the lab to pass that back, and so.

So that's essentially what we're trying to sort of define, there.

DR. LAYLOFF: Anything else on that? I think we've already separated it, I think.

DR. SHABUSHNIG: Just one point of clarification from your talk earlier, Ajaz. With the sort of concentric rings of overlapping systems, and I agree with that model what you're showing there, but what you're saying, if I interpret it correctly, is that it may be appropriate, if you are missing some data in one of those areas, that you still have sufficient information to release the lot--to judge lot quality based on information that you have from other systems. Is that correct?

DR. HUSSAIN: Right, I mean, I think a measurement or a sensor would be part of the system not the whole thing, definitely. And so, the built-in redundancy and so forth, would essentially define that the system is adequate to do a continuous verification of your quality so that lab-based testing in some cases may not be necessary for release.

DR. SHABUSHNIG: But it's not just redundant sensors, it's really that you have other

kinds of information that is still sufficient to--

DR. HUSSAIN: Correct.

DR. SHABUSHNIG: --assess the quality of the overall batch?

DR. HUSSAIN: Correct.

DR. SHABUSHNIG: Okay.

DR. HUSSAIN: Sort of to elaborate on that, let's suppose you are looking at blending as a unit operation. You, in your development, have identified a blend time and have developed an SOP. Now, the SOP requires a operator to load the powder materials in a certain order. And so, if you have an online sensor to assess blend homogeneity, it actually is very fine that the SOP was carried out correctly and so forth. So that--its use could be verification of that step and probably build or collect information for the next step, maybe link it to dissolution. So, that's how we would sort of view that.

DR. SHABUSHNIG: Thank you.

DR. HUSSAIN: I think the distinction between that--this concept and parametric release, I think Bob already, sort of alluded to his thoughts on that and that reason that I sort of put this on is, I think, we are moving towards some