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FOOD AND DRUG ADMINISTRATION

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wtk

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

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Ajaz Hussain, Ph.D.

Committee Members:
Thomas Layloff, Ph.D., Acting Chair
Gloria L. Anderson, Ph.D.
Judy P. Boehlert, Ph.D.
Arthur H. Kibbe, Ph.D.

SGE Consultants:
Melvin V. Koch, Ph.D.
Robert A. Lodder, Ph.D.
G.K. Raju, Ph.D.

Guests/Speakers Participants:
Eva M. Sevick-Muraca, Ph.D.
Leon Lachman, Ph.D.
Emil Walter Ciurczak, Ph.D.
Kenneth R. Morris, Ph.D.
Howard Mark, Ph.D.
Thomas Hale

Industry Guests/Participants:
Efraim Shek, Ph.D Ph.D.
Ronald W. Miller, Ph.D.
David Richard Rudd, Ph.D
Rick E. Cooley
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Henry Avalllone, B.Sc.

Open Public Hearing Speakers
Justin O. Neway, Ph.D.
Li Peckan
Allan Wilson
Dan Klevisha
Tom Tague
John Goode

C O N T E N T S

P R O C E E D I N G S

DR. LAYLOFF: I would like to welcome you back to the second day of the Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science.

I would like to have our meeting statement from Kathleen.

MS. REEDY: This meeting statement is acknowledgment related to general matters waivers for the Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science.

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. Boehlert, Dr. Koch, Dr. Raju.

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.

This is for June 13, 2002.

DR. LAYLOFF: Okay. Now we'll go around the table and introduce ourselves and our affiliations starting with John James.

DR. JAMES: 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 for the Center for Advanced Sterile Technology for Pharmacia Corporation.

MR. COOLEY: Rick Cooley from Eli Lilly.

MR. CHISHOLM: Bob Chisholm, AstraZeneca.

DR. TIMMERMANS: Jozef Timmermans, Merck and Company.

DR. WORKMAN: Jerry Workman, Kimberly-Clark.

MS. SEKULIC: Sonja Sekulic, Pfizer.

DR. SHEK: Efraim Shek, Abbott Labs.

F DR. G. ANDERSON: Gloria Anderson, Morris Brown College.

DR. KIBBE: Art Kibbe, Wilkes University.

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

DR. LAYLOFF: Tom Layloff, SGE with the FDA and with Management Sciences for Health.

DR. BOEHLERT: Judy Boehlert. I have my own consulting business.

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

Washington.

DR. LODDER: Rob Lodder, University of Kentucky.

DR. SEVICK-MURACA: Eva Sevick, Texas A&M University.

MR. HALE: Tom Hale, Hale Technologies.

DR. MARK: Howard Mark, Mark Electronics, also an independent consultant.

DR. MORRIS: Ken Morris, Purdue University.

DR. CIURCZAK: Emil Ciurczak, Consultant.

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

DR. HUSSAIN: Ajaz Hussain, CDER, FDA.

DR. LAYLOFF: Thank you very much. We had a very productive day. We gained some time on our schedule. I think our working groups made good progress, and we will reconvene those this morning and continue those discussions for the morning.

I think, Ajaz, did you have anything that you wanted to particularly emphasize to them?

DR. HUSSAIN: There are sort of three things in my mind: one, starting with education, the training program working group. If, for example, you go through the outline and what I

would hope is that you would sort of define the learning objectives more so than the details of the curriculum itself, in a sense I think that would really help us to frame the broad requirements and focus on what--how do we arrive at the right questions. I think that's--if you could summarize that today, that would be wonderful.

And with respect to process and analytical validation working group, I think this would be probably one of the most important aspects for the guidance development process--the general guidances--what type of information--keeping in mind this is a general guidance without much technical details. I think one of the frameworks under which we could sort of define validation--validation for intended use, I think Moheb had some suggestions, I think he'll bring those to the committee this morning. And sort of the rational approach to validation. Because my personal belief is, I think, the GMP are so critical that we really need to have good GMPs to ensure quality because endproduct testing is so limited. And I think the challenge to our inspectors has been in the sense their workload and their responsibilities so huge, I think if we can bring rational science with using

PATs to manufacturing, I think that would be wonderful because without GMPs, I don't think we have a quality system so validation and qualification all are extremely critical elements of the whole quality assurance system.

So, I'm looking for sort of an approach for how would we validate PATs in a rational sense and what sort of information should be sort of brought to bear on evaluating these technologies. So if that is the broad focus and some of the questions we posed and some of the questions we provided to you, if you go through those I think it will be very helpful for us to have a summary of your thoughts so that the general guidance might include a paragraph or two paragraphs on general principles for validations of PAT.

In terms of process and product development, I think the concerns that have been raised have been with respect to delay in NDA approval because of a new technology coming in. And I think those concerns, in my opinion, I think there are, certainly, basis for that but should be ill-founded because FDA is willing to work with you throughout the process and, in fact, what the offer on the table is we could set up special meetings at

the end of Phase II and so forth to simply discuss some of the new technologies so the fear of delaying NDA approval is removed.

But at the same time, I think the aspect that I'd really like to sort of bring in is I don't think the supplement process is an ideal process for having innovation come in because a lot of these things have to--if you had prior approval supplement for everything it holds things back. And the concept that we're trying to develop is a team approach--a review and inspection team--so my hope is a lot of these implementations could be in an annual report type of a format, rather than a supplement. So if a company is willing to invest and go through and apply new technology in the new drug development itself, one could imagine that we could sort of essentially establish interim specifications for the approval process because you essentially have the traditional testing for validation and so forth. So, essentially for PAT, you have interim specifications and we agree to those, and essentially at some point when submission data is collected those become the rule.

So let's think differently--out of the box--in terms of how to facilitate new drug

development using PAT, as well as in terms of validation.

So it's a big task and the challenge is the general guidance will have to have language which sort of reflects the positive win/win aspect of this and not be perceived as cumbersome, bureaucratic, and so forth. So that's what we're looking for.

DR. LAYLOFF: I'd like to reinforce a couple of those comments. I think for the training, I think the way that this probably should start out is what are the required competencies that these people should have and that's the training objectives. And I think the target should be to have the competencies required to satisfactorily perform their assigned duties, which would be reviewing and inspection of these techniques, and the target should be a certification so it's a nice little consistent-type function so that people do have--are credentialed that they have achieved a certain level.

The other caution you see is when you start moving to new technologies is everyone starts to move to the realm of the possible, rather than the realm of the probable. And if you start moving

to the possible, you become paralyzed. Certainly, the disaster of September 11th does not mean that we should start designing all of our buildings to be hit by planes loaded with fuel. That's a possible but not probable, and if we look at the regulatory history that the FDA has had with our industry, the probability of having significant fraud is very minimal. The people are very conscientious; our industry's very conscientious. So when we look at validation issues, integrity issues, we should look at probabilities rather than possibilities.

The other thing I think that would reinforce what Ajaz pointed out, if you think you develop an NDA and you throw it over the wall at the end at FDA, it is going to be delayed. On the other hand, if you take him up on his offer, with his skilled staff and the trained people to work with them so that everybody understands what you are trying to achieve and how you're trying to achieve it, it will facilitate the whole process.

So I would ask that you keep focused on what is probable and not what is possible so we can keep moving forward.

We'll adjourn now, back to our committee

meetings, our groups. So if you could go back to the groups--same rooms?--in the same rooms that we were yesterday, and we will have a break at 10:15 and you will reconvene with your groups until you complete your efforts this morning. Thank you. Oh--

DR. KIBBE: When do you want to regroup here, because I think we will finish a bit early so we can wrap this meeting up maybe by 3:00 or so.

DR. LAYLOFF: Would you like to come in--would you like to start to convene at 11:15 for sessions here?

DR. KIBBE: What I was hoping is we could reconvene here immediately after lunch--

DR. LAYLOFF: Okay.

DR. KIBBE: --so that each group has time to make the summaries and so forth.

DR. LAYLOFF: Okay, that's good. One o'clock would be fine.

DR. KIBBE: Okay.

DR. LAYLOFF: So we will go through our group discussions and reconvene here at 1:00 o'clock for wrap-up. I will not be able to be with you this afternoon. I ended up terribly conflicted in my schedule, and Dr. Kibbe has agreed to take

the helm and take you to conclusion.

[Recess.]

DR. KIBBE: [Presiding] I thought we did really well yesterday, but maybe I'm delusional. Or, perhaps, we needed to put a process assessment tool in place to see how well we're doing. Each 15 minutes we decide if we said anything worthwhile. I still like assessment rather than analytical because I think it gets us away from remembering how to do titrations.

Yesterday when we broke, we had some people who had agreed to begin our thinking towards a document that could be used by the agency to formulate its guideline on validation. I think we've come to some good conclusions. I don't think anybody would disagree with the fact that we're not going to come up with 42 different validation documents for 42 possible technologies but, rather, a guideline where a company who has a technology that they have faith in would use to go forward to make a case for the agency. We have, I think, discussed the fact that you can't validate a process very well if you don't even know what process you're trying to validate, and we have a colleague who has some introductory paragraphs or

sentences ready. He's hiding down there.

MR. LEIPER: Not quite hiding, Mr. Chairman. I like your use of words. I don't think that we agreed to do anything. I thought we were directed to do something, so we've actually met that aspiration of yours--well, I've tried to do that.

I think that the other point that I would certainly subscribe to you that you've brought up just now, I think that that terminology that we use about process assessment technology might actually be an awful lot closer than analysis, and if we go back to where we started yesterday, I think the reason that we went a bit off track to start with is that we started thinking about chemical analysis. And that is not what it's about.

So I'll try and summarize. I've got some bullet points and we can see how this works out, and I'll get them over to Rob as we go through and we can put them on the screen.

The first issue that we tried to address, I think, was the background, you know, where we are now, because if we don't actually have a datum point of where we are now, of where we think we are now, we won't know whether we've improved or not.

And from that the first bullet point I've got is that, whether we like it or not, existing validated measurements invariably correlate poorly with process performance. So there are two issues: one, the measurements that we make don't correlate; and, two, they're validated. And so if we're going to use that type of validation as our background, we might just be disappointed. So that's where I think I started yesterday.

I also made the comment that univariate measurements are used to infer compliance of dynamic multivariate systems. And that's what we do; that we measure what we can measure not what needs to be measured. That measurement needs to be--well, it hasn't been seen a process-related; there's actually been a divide between the process and the measurement. Measurement is product-related rather than process-related.

That measurement needs to respond to process needs over the product life cycle, so it's not a one-off operation. If we want continuous quality improvement, it's got to be dynamic.

And to do that, we need to understand the process, and the last point in this slide would be that we've also got to recognize that the

conventional approach to validation might be limiting or, indeed, inappropriate.

So, do these bullet points sort of ring bells with you? Does that sum up where we started yesterday?

DR. KIBBE: Anybody? What we're going to try to do, when we have electronically validated our system, is put those bullet points up there so people can read them and say, ah, that's one's--no, I'd like this worded different and that different, okay?

MR. LEIPER: Yes.

DR. KIBBE: I think there's a lot of what we agreed to in what he said, and I want to give you an opportunity to say, well, I didn't quite agree to that statement, but it's close to what I agreed to and we'll wordsmith it.

This would constitute our attempt to helping the Agency write a preamble to why we're even going in this direction.

MR. LEIPER: Precisely.

DR. KIBBE: And what have you. While he's still arguing with the equipment, Jerry had--

MR. LEIPER: Okay, I've got the next one that we went on to, Art, and then Jerry's would fit

in after that, I think, if I may. Excuse me.

DR. KIBBE: Excuse me, go ahead, my fault.

MR. LEIPER: Okay, then we went on to talking about understanding processes, and if we want to understand processes, we've got to break them down into their unit operation--the unit operations and begin to understand them individually and, indeed, collectively, if appropriate.

So we break it down into unit operations; we assess the risk potential from each unit, individually and collectively where it might impinge, two might link together, using techniques, for example, experimental design.

DR. LODDER: May I break in for a second?

MR. LEIPER: Yes.

DR. LODDER: I think it would be a lot easier if everybody who has written text could move over to that microphone so I could look off of it while you were reading. I thought we'd just keep things going faster.

MR. LEIPER: Okay.

DR. KIBBE: Or if you could give him your first set and he could type in--

DR. LODDER: Okay, well, whatever.

DR. KIBBE: A couple of you had--you have it electronically. Okay, so--Tom, you had something electronically? Good. All right.

MR. LEIPER: So, you know, that's what we would do; we would address the risk potential. We would then--we'd be looking to design systems to manage the risk, and that could be univariate measurements, it could be multivariate systems. It could be anything, but it would be certainly directed at what the need was.

We would then develop systems. The next step would be to establish proof of concept. And then to challenge, which would be conventional validation. But this is all related to the design of the system. It's not--you know, we just can't pick it out of the air.

And the objective is to confirm that processes--is to confirm process and measurement validity in real time across the life cycle of that process.

And then I thought that's where Jerry's list of bits might fit in, but that was where I got to.

DR. KIBBE: Anybody have a comment about what...

[No response.]

DR. KIBBE: I have one little aside. Listening to you, it sounded like you were describing changing from what we have to a completely assess process from beginning to end, and I think what we're going to see is segments of the process being assessed with, you know, technology being--and then that growing across lines of production.

MR. LEIPER: I agree entirely with your view of it. I see it--I don't--this is what our overall objectives would be and it would be the journey to get there and I think that's where--

DR. KIBBE: All right. We're starting to see some of your words up on the--

DR. NASR: Art, I want to make a couple of comments.

DR. KIBBE: Sure.

DR. NASR: These are intended to be general comments, but may I address some of the validation issues we are dealing with. I spent time reading the transcripts of the meeting we had in February, and I decided to stay completely silent yesterday because about half the comments I made myself about validation when we met in

February. Sometimes when you listen, you get a bigger picture and better understanding of what's going on.

I think two comments, good comments, were made yesterday: one about the validation of the process need to be done after we understand the process. And the data and the information gathered during the process development is just useful to develop the process and the process needs to be validated only after complete understanding of the process taking place. I think that was an excellent comment.

Another comment that was made by Rick Cooley, and Rick and I discussed it substantially afterwards, and that is the focus of validation needs to be on the intended purpose to make sure that the measurements that we are making are suitable for the intended purpose only. And we do not and we should not focus on validating the technology itself or the device, whether it's analysis or an instrument, because if we do that, we will not be able to achieve what we are being asked to achieve.

So because of that, my suggestion would be, for the purpose of a general guidance, that we

have three paragraphs: one paragraph simply to state that validation needs to be tied to the intended purpose to make sure that the suitability for the intended purpose.

The second would be to outline major validation criteria that must be achieved no matter what application or measurement we are dealing with. We are talking about robustness, we are talking about suitability, and all the things that most of the people in this room are familiar with.

And the third paragraph simply list available documents and guidances available such as ICH documents and the agency guidances on analytical and process validation where we can lean on and abstract and gather information that we can use.

Again, in summary, I suggest that we make our validation input into the guidance to be simple, general, and without going into too much details because if we go into details and try to provide validation criteria for all possible measuring devices, I don't think we'll achieve that.

Thank you.

DR. KIBBE: Are those your words?

MR. LEIPER: Yes.

DR. KIBBE: Good. We're starting to get to where that is. Does someone else have--he's got yours, too, right, Jerry? Then we're going to start putting them in order. Yes, sir?

DR. WOLD: Just a short comment to Ken. It seems that Ken is very much focused on validating the process. I think we should perhaps discuss the two. We have the validation of the process which is necessary in the process, and when we use process in manufacturing, but we also want to validate that PAT measurements give information about the quality of the product. That's two different things. And, as Ken says, the quality measurements made for the products do not necessarily correlate well with the measurements for the process, but they're still needed. So we have two sets of objectives.

DR. KIBBE: We could certainly divide it again and say that we can validate a process, but we also have to validate the instrument we're using to measure the process, and then we have to validate whether those things are all resulting in a product that's what we wanted. And we could even go as far to say how do they help us understand the

endproduct quality.

MR. LEIPER: I think it's not coming off. The objective is to confirm process and measurement validity in real time across the process life cycle. I mean, that's what we are trying to do. If you remember, the very first statement I said is that we do use validated measurements today, but they don't correlate with process performance. So as you go through these two slides, that's the transition. And I agree with Sonja all the way that we've never seen measurement validity and process validity actually looked at in the same context.

DR. KIBBE: Thank you.

MR. LEIPER: And I think that the point you make is actually a good one, and what I was trying to do in terms of the unit operations, et cetera, is that we heard a lot about risk-based assessment, but when we were talking about risk-based assessment, the quotation yesterday was about safety and efficacy, it wasn't about processes. Processes are what deliver safety and efficacy. So I think that we've got to take risk-based assessment and FDA's got this in their HACCP procedure. It's actually sitting there.

It's just that we don't choose to use it. But that's a very good way, a very good methodology for beginning to understand what the variability is, as Sonja would prefer to see it called, or risk. Because that's what we're trying to do in processes: we're trying to manage that potential variability out.

DR. KIBBE: Do you want to comment on what's being miraculously presented to us here?

MR. CHISHOLM: I think the first point is that this is a general gauge so we can't be too specific. So I'll try to keep--other statements from yesterday a few thing that I said, and I said I'd do that last night.

The first one says the validation protocols will be different depending on whether you're dealing with a new product or an existing product. It's a very, very different thing that you have to do. Because a new product has probably, hopefully, been designed with manufacturability and all these principles in mind; whereas existing products haven't. Okay.

So when you apply PAT retrospectively, I think you probably will have different validation protocols than you have for new products where

you've been sinking it into the process all along.

The second point is I think that your validation plan really needs to reflect the holistic nature of the system that you're in. If you have actually got a system where you've got real-time quality control and real-time quality assurance for the product coming off at the end all statistically based, that's a very different situation for someone who's sampling occasionally outlying even using these techniques.

And so, you've got to remember that if you have what I've just described, RTQC, RTQA, then what you do is, every time you manufacture a batch, you essentially revalidate your process because you're monitoring through both the QA and QC. So that's a very different situation from the one where you're occasionally sampling. And we don't use the word "statistically" often enough, I don't think.

I think the second one's a very important point that we haven't touched on, and it's going to be very, very important for the FDA, as well as the industry. There has to be some measure of yes or no, even though it's always going to be maybe.

You've got to be able to see why you

passed something and why you failed something. So I think that your validation rationale has to find some way of establishing that so that when you go to predict in running a manufacturing process you can justify it yourself to the authorities that you are actually in compliance and why you took that decision. And I think that's quite a gray area, and I think it has to be addressed in some way.

Okay. Those were the three things you asked me to do yesterday.

DR. TIMMERMANS: I just wanted to make one or two comments. I fully agree with what Ken and Bob have been saying so far. But I think we should take a look at what reality is. I suspect from experience that we will be implementing process analytical technologies first sparsely, and then later on we may design our processes around it.

I think what we need to do is realize that and really provide guidance in the area of how to implement--maybe, you know, we would start with one unit operation. If I look at some of the processes that we've used process analytical tools that we haven't used it in each unit operation, rather we've picked those that we felt needed the technologies and implemented it there.

So, I think the overall approach is correct and is a lofty goal, but I think the reality is that we will be implementing them in just bits and pieces. So I think the guideline needs to address how to implement it in such cases, not only for new products--and I think even with new products, if we're designing our processes to be able to--to accept these process analytical tools and marry the two, there's still the need and certainly, I imagine, a significant number of applications will be applied to in-line products because we know we have problems with in-line products. So I think that's something that the guidance needs to address. Not only the overall heuristic approach, if you have a new product and you have every opportunity to implement it, but just also on a case-by-case basis or on a case-by-unit operation basis, if you will.

MR. LEIPER: I agree entirely with you. I think one of the problems that we've got when we talk about validation just now is that we've got a statement about validation that the process will be fit for what it's intended or, you know, something like that. I think that what we're trying to do here is to get behind the method the basic

systematic approach, and I've been in a similar situation and I think that what we do is that we've got a problem, we then say, why have we got a problem, and we identify the risks, et cetera, and we go through it in a pretty logical manner.

Now, what I'm concerned about is that I don't think that we look at a lot of validation from that logical perspective. And I think that if we give people a systematic approach to validation, they can plan their scientific response against that systematic approach; whereas, as it stands just now, there's no such thing as a systematic approach. Different companies have different--you know, they look at it in different ways and come up with similar types of solutions, but it's a systematic approach that could be agreed between industry and the regulators for how one addresses these problems that would probably help to take us forward.

DR. TIMMERMANS: I fully agree.

DR. KIBBE: Anybody else?

MR. CHIBWE: I think Ken's comments, as well as Bob's comments, I see them as very valuable for making the foundation for process and analytical validation; and if we could use those

principles to tie in with what Tom and Jerry pointed out yesterday--and I believe they're going to present some of that today--where we could differentiate from batch process, as well as continuous production process, and then we also have to use the intended-use validation approach, not necessarily always going back to the traditional validation approach which is going to tie us down.

So I think if we use those as the basis and foundation, we'll end up with very good guidelines at the end of the day.

DR. KIBBE: Anybody else?

DR. MILLER: I think we'd probably all agreed that what Ken said is the goal, and the question is probably how to get there; and partly how to get there is where we're going to start from how we're going to approach it. That's why yesterday I made a comment, is it reasonable to start from the current validation paradigm, and my thought then and it's still my thought now was that in terms of actually implementing it in practice, the people involved both, you know, from the top level all the way down to the field inspectors would probably be more comfortable if we had a sort

of a revolutionary approach outlined, rather than, you know, just all of a sudden changing the whole paradigm suddenly, so they'd start from somewhere they're familiar with and there would be a greater comfort level and, therefore, a greater acceptance level of the new paradigms.

And I think one of the things we should try to think about, you know, during our session this morning is the path to get to where we want to be at.

DR. KIBBE: Does somebody have a path?

MS. SEKULIC: Not necessarily. I do have a comment, though. I concur fully with Nasr. I did a lot of talking during the last session. I think we covered a lot of good territory. I'm not convinced that we're not overcomplicating the situation. Okay? I'm going to try and challenge a few thought concepts here. Separating the two validation--into two validation approaches, one for pre-, one for post-, may not necessarily be the right thing to do. If you validate before or after the NDA, we're still concerned about the appropriateness for intended use. Therefore, the same logic, the same sequence of actions, methods of element, identification of sources of the

variability, identification of critical parameters, control points, followed by validation of those and, thus, the documentation of that, we're done. Don't we already have the pieces and the framework in place? Are trying to complicate things too much by raising PATs to a new level of scrutiny which may not necessarily be warranted?

DR. KIBBE: And what do people think about that? We're very quiet this morning. I think we need to make you run around the table. Yesterday we were so fired up. Did you have a long night or something? Go ahead.

MR. MADSEN: Yeah, I totally agree. I think that we've been--in a perfect world, which we don't have, we should have been validating methods and processes this same way all along, and I realize that maybe, you know, back several years ago we weren't but, certainly, the goal is to validate the method, to validate the process to do it in a logical, sequential way. And I don't see where PAT would be really any different. There may be some differences in multivariate versus univariate analysis that we have to worry about and maybe some of the methods are different in themselves, and maybe because of the method

differences there might be some little quirks we have to deal with, but basically validation is validation.

DR. KIBBE: Is this a good time for Jerry's list of things that are important in a validation process that apply to any validation process that we could just put in here and reiterate and say, guess what, you've been doing this and these are what we really still want?

DR. WORKMAN: Well, as Professor Lodder has magically projected on the screen, this is just basically a laundry list of things that have to be rationalized or addressed in the validation process, potentially, at least.

Going through the sensor validation means the box itself in the sampling system. You have to know that the integrity of that is maintained. Then the software validation, including any multivariate algorithms, you just have to say what you're doing and verify that what you say you are doing is what you, in fact, are doing.

Sensor calibration and calibration transfer validation. Once your software and your algorithms in your hardware are validated in terms of operation, then you have to take a look at what

you're doing with that, which is generating models. Those calibrations have to be evaluated in relationship to what you're measuring to make sure the integrity is maintained and that you are, in fact, reporting what you think you're reporting.

Also calibration transfer, it's not just important from one instrument to another, but that instrument will inevitably fail and you'll need to put that calibration back on the instrument after repair. So you need to demonstrate that there's a lot of integrity in what you're doing there. And then the process-monitoring protocol, batch versus continuous, is basically that as you're monitoring the process, you need to demonstrate that, in fact, you are measuring what you think you're measuring, where you think you're measuring it, and rationalize that whole issue.

And process modeling, in order to study the process, you have your basic thermodynamic models from the textbooks and engineering training. You need to take a look at that and see how true that is because oftentimes we know that when we look at real information it's much more complex than what we thought.

And then the process control protocols,

when you're getting this good information from your system, what exactly are you doing with it to control the process and make sure that the end product is what you think it is.

And then the data management and storage protocol, how are you going to maintain that data and be able to display and demonstrate what you're doing at a future time.

Next slide please.

And then if we're looking at--if we're just trying, again, make a list. If we're looking at types of methods, you have a primary method where you're actually analyzing directly the analyte and you don't need any secondary or backup methods to verify this method, so it has specificity and selectivity that are appropriate.

And then a secondary method requires a primary method to validate it so, in that case, both methods would have to be validated. And then, in terms of analyte complexity, you have direct measures, which might be an active ingredient; indirect measure is something like dissolution, which is a property based on composition or physical properties which can be measured directly, or some virtual measure which is, you know, cost of

production or customer satisfaction or quality index or something. So those have different considerations involved with each one of those.

Then we also were talking about dimensionality in terms of univariate/multivariate which are quite different. And then there was another list--next slide, please.

Just on the implementation side, I believe a thorough document would have rationalization from a scientific basis on the following points and maybe more but, you know, what information is needed and why is that needed? Where is that going to be taken in the process? What are the sampling points? And when and how often are the measurements needed and the rationalization for that? And how is this information that's received from this whole validated measurement system, how is that going to be used and the rationalization behind that?

And then, who's going to interpret that? What group or training is required to interpret that information and how is that used? So the whole rationalization behind that.

DR. KIBBE: Thoughts, anyone?

MR. LEIPER: I think there is a point of

contention here and, again, it's a view of what is a primary method. Now, and people say, well, this is a definitive method, but often you find it's the first method that you thought of and it's actually knowing whether our primary method is capable of doing it. It's one of these things that got mixed up over a period of time. And if your primary method doesn't--if the primary method that you've got doesn't actually correlate with what you need to measure, then you've--we've got ourselves a problem.

And I think that brings us onto the complexity, and I wouldn't see this being--I don't see it being overcomplex or anything like that, but if you think of blend uniformity, we would probably tend to go to an endpoint. You know, so we wouldn't necessarily need a primary method or--

DR. WORKMAN: Of course, when you flesh these things out, you get a better definition. I think primary method indicates that you don't require any other method to validate or verify that. So, in that case, that would be a primary method.

MR. LEIPER: No, I agree with that, but that's a mindset away to what we--you know, what

we've used to today, I would suggest. Is that a mindset away from FDA thinking or--

DR. NASR: I think so.

MR. LEIPER: And I think it's about capturing that because that's the way we'll get simplicity, to get away from the current mindset, I think.

DR. TIMMERMANS: I think what Jerry just has shown in my mind validates what Sonja said before. In my mind, this approach as laid out here is not very different, if not different at all, than what I would expect we do for any analytical method or any measurement we do right now.

DR. KIBBE: No, I couldn't agree more, I think one of the things we're talking about is, because it's a new approach, everybody's got these little ooh-ooh kinds of feelings; and as we get closer and closer to understanding it, it isn't anything new, it's a new way of doing a better job of what we're good at, and we use the same logic and same science to validate what we do.

I think, if you look at his list, and an example of primary is the active ingredient. And when we talk about blend uniformity, we used to talk about the active ingredient. And now we don't

want to talk about just the active ingredient; we want to talk about all of them.

Well, this is a step forward in our understanding of what we're doing and controlling what we're doing. And if that happens to be our new measure and we have a way of doing it that allows us to comfortably come to an understanding of blend uniformity in terms of all of the ingredients near IR or something else, then all of the ingredients are the primary measure or the blend mix is the primary measure and we go on. And so I agree with you, I think that we can agonize over this, and one of the reasons we need a guideline which lays this out is because our colleagues, in an absence of coming to these meetings, are going to wonder what we mean and how complex we want it to be. And if they see the same thing they've always been doing, they might have more comfort in moving forward.

MR. MADSEN: Having said all that about blend uniformity, you can have a perfect blend uniformity--I've seen situations where the blend is uniform, but during the transfer process into the press or because of certain press considerations, the finished product may not be uniform or may not

have the desired content uniformity. So we have to make sure we build this in.

MR. HALE: I agree with the statements that we are building on a foundation of validation, and I like the comment that Ken made yesterday and if I could restate it or in my own words, perhaps, that there are layers of validation that we go through. We start out with IQs and OQs in process, and in my mind the foundation parts of validation are really no different. Maybe they're a little more complicated or complex, but the thought process is the same, that equipment works, that sensors work, and that we have some way of justifying that we feel comfortable that equipment works and sensors work.

Where this does, I think, get us into a different realm, perhaps, is at the very top layer, when we start thinking about how our product is being released. And I think that there are potentially different ways to release product with additional technical capabilities and additional mindsets, and I think there are three of them that are up on the board.

The first one is pretty much what we do now, where we have a fixed set of parameters to

manufacture a process and, subsequent to manufacturing--and this can be thought of not only in release of product, but release of product from one unit operation to the next so it encompasses both, I think. And that the release is subsequent to this manufacture by some external physical/chemical testing, that we run a unit operation or run a manufacturing process and then we test it, and based on that data, we then release the product from where it is.

The second condition is that--I'll just--you can read it as well as I, the product is manufactured according to certain process conditions that have been shown during development and manufacture to infer product performance. So that there is somewhat of a--that we believe we understand our product and process enough that by measuring the process itself, we infer product quality and that there are relationships that are developed and confirmed with external physical and chemical testing to verify that.

The third one is that we're actually measuring a product quality itself and that by measuring the product quality itself, then the process can be optimized and, back to what Bob was

talking about, that you can actually learn about your process and change it and as it goes along, as long as you understand your product quality, that your process can be optimized and so on.

And I believe these are different ways of releasing--and at this level, not at the equipment level or sensor level, but at the product level, the meaning of validation changes, potentially changes, that instead of having three lots at a static condition and calling the rest of the manufacturing life cycle good based on limited testing that as you increase your sophistication of understanding of the product and the process that in some ways the product validation goes away in the ultimate realm of this. It at least changes dramatically in its concept at the product level.

And that, perhaps, this could form a basis of deciding what validation means and differentiating between what is currently being done and the potential of the future as we add on these PAT technologies.

DR. KIBBE: Anybody else?

[No response.]

DR. KIBBE: I think getting back to your point, there's always been concern about

measurements made during a continuous process being the right place to make the measurement and the right place to determine whether or not you should go forward. And I think what you're saying is that even though at some point we think we have a uniform product and we're ready to go, that doesn't mean that we have to stop watching that. And I don't think we've said that. I think what we're saying is that if we have a new method of looking at blend uniformity as we blend, then that's a good thing to use to know that at least at that point in our overall process, that particular process is well under control.

And then if another problem comes up--and I think that brings us back the fact that we are not prepared, I think, to throw out end-stage testing on any of our products until we have the whole process under control, but, as we, I think understood a little earlier, people aren't going to be able to put the whole process under control by turning a switch. And so we're going to do it bit by bit until we've finally gotten there. When we get there, then end-stage testing might or might not go away. And I really don't think it'll ever go away because behind it there's stability testing

and that's really hard to do with PAT because it's a different kind of process, and that relies on our looking at and analyzing the product itself.

So, how many of you think that the ultimate reference for validating a process could very well be the endproduct analysis?

How many of you think that the ultimate way of validating an interim process or a process technology is the endproduct analysis? If I have a method that guarantees or looks at some stage in the process and I can do things to it to make it show that that is out of control and I test my product and the product is no good, and I do it and it shows that it is under control and my product is good, is that an ultimate--can we ultimately rely on that to validate our process?

DR NASR: I don't think so.

DR. KIBBE: Okay.

DR. NASR: And the reason is, when you do endproduct analysis, you do not analyze every capsule or tablet you are manufacturing. So it is a sampling issue.

MR. LEIPER: There's only one instance where we actually do that and we're not very good at it, and it's using USP-calibrated tablets for

dissolution. We do 100 percent testing on them, and we occasionally get billets-doux from USP to tell us that they've had a problem with that batch of tablets.

DR. NASR: Right, how often--and that happens very often.

MR. LEIPER: And that happens very often. So if one wants a living proof of the problems that we've got, that is certainly one of the markers.

But I think the other thing that's interesting is that--and it's been brought out this morning--that we haven't changed our post-validation very much. What we've changed is our appreciation of what the need of the measurement is. That's what's changed and everything else has got to match with that some way or another. And it will happen by attrition. It will be units that we put in and it helps us with problems. There's absolutely no doubt about it. But I think from a lot of what we said yesterday, and it's been captured, you can certainly pull that out of what we've captured, I think.

DR. CIURCZAK: There was one comment, I think, that Arthur had made even that we're going to be doing the same type of thing. We're going to

get numbers. Going back, Ken made an interesting comment to me yesterday, that when we talk about blend uniformity--and people are used to seeing HPLC data 97.8, 99.5, all this. And I had this same problem back at my last place of employment where one of the people doing the work in development wanted to see numbers. And, as Ken said, well, the principal components are numbers, things, like this mahalonova's [ph] distances are numbers, but it doesn't require if you do--and that was, I guess, Pfizer's first thing that came up years ago where you just look at the variation until it's a minimum standard deviation. You don't require the thing we've all agreed upon is crummy is actually putting a thief in and pulling it out.

If you want numbers, quantitative assays, so that you feel comfortable that that's what you always got before, then we're going to be taking a very elegant way of nonintrusion and in having to use an intrusive method to do it. So we have to be careful--we have to do education that you're not going to see this. You're going to see numbers, but you're not going to see the same numbers.

So it's a feel-good thing. You know, I think the biggest problem we had with a validation

on a tablet is we had to make it look like an HPLC, we had to--before Gary and a number of people here worked on NIRVWOG committee to come up with the new USP proposal, the first thought before that happened that Gary and I would be playing with was can we use the same terms to make it sound like HPLC because the FDA doesn't need this, our own RQA needed it before we could ever get it approved. And I think we spent six months getting it bounced back because something that was in tabular form, they wanted to see in prose. And then something else they wanted to see as a footnote, and then, finally, I sat down with the director and said, Is there anything in here that's violating our SOPs or a CGMP or any FDA or any guideline that you can point out? Or is it just something that you haven't seen before? And three days later we got the approved package back. She was honest enough to sit down and say, yes, it's just because it's something I haven't seen before, I can't find anything wrong, technically.

So we're going to need to do that because if we try to be feel-good and do a blend uniformity, going back to that again, and when we have to start probing and doing HPLC to validate

our NIR, it's very much like using a sledge hammer to validate microsurgery, that the error is orders of magnitude greater and we're not going to prove anything.

DR. TIMMERMANS: Gary, while you walk to the microphone--Emil, I think what you're saying just comes back to what, I think, we emphasized yesterday that everything is based on scientific rationale, not necessarily numbers but scientific rationale.

MR. RITCHIE: Art had gotten onto something, and, Ken, I wanted to pick up off of--regarding a specific example of an endpoint measurement that we currently make versus what we're doing when we're looking at the process. I already have quite a dossier of documentation for a process development where they've purposely changed certain components to determine if, in fact, my dissolution profile is going to be the same at the end of the development.

They change, let's say, one constituent. The product development people know exactly what that constituent is. I come along and say, hey, rather than doing the dissolution at the end, I can actually tell you during your development stage,

using principal components--okay--what those certain components are going to be so that you can go and physically change them and I can correlate them now to a new measurement, i.e., principal component.

Well, you put that in the package and you submit that. The question now becomes is how am I going to convince my regulatory people and how are they going to convince the FDA that what we've looked at with this new measurement in changing those constituents are equivalent to the dissolution measurement at the endpoint. I think that's what I'm seeing going on here. That we're finding--that it's a problem to reconcile this endpoint measurement that we're currently doing in development versus what I'm showing them to do in real time during development.

I'm saying they mean the same thing. How? How are we doing that? That's what I think we need to focus on.

MS. SEKULIC: But that goes back to the education question, okay? There is no doubt that there is a lot of education that we're all going to have to go through, both industry and the regulatory authorities around the globe. But,

again, if we can't make the science stand up on the basis of good science, if it's not defensible science, then we probably shouldn't be doing it.

I think what we're all saying is that this is defensible, validateable science that is going to be telling us a lot more about our processes and that's what we need to focus on. Yes, there will always be people who won't get it, who won't want to get it. But should that be the stopping point? No, I don't think so.

DR. KIBBE: Let's get back to our task, which is to help the agency come up with a guideline for validating these kinds of things. And the more and more I hear, the more and more I say to myself, well, we don't need anyone, they've got guidelines for validations, let them use the old ones.

T2 I have a feeling that that's not going to be a good answer for the industry because the industry isn't going to be that comfortable with that, and they'll want something from us that is both encouraging and empowering and gives them a place to start and a place to go and those who sit around here who have listened to the discussion have that and those that haven't been here don't

have that and so on. I think we're going to end up with a new guideline or a new guidance document regardless. And the question I have for you is the information that we've already put together that we've seen up on the board, is that enough information? I think there's one other suggestion in that we put in references to things like ICH and other places to go. Perhaps we ask the agency to cross-reference to current validation documents for different kinds of processes so they could look at things that would be similar to what they're trying to do, those kinds of things. Is there anything else that we need to include that would be helpful?

DR. MARK: Well, there are certain places where you can point to where we know that the current guidelines would fall down, and one example that comes to my mind is, for example, the question of range. I mean, the--you know, the standard requirements from ICH and so forth say under various conditions 85 percent, 115 percent of target value and so on and so forth. And if you have a product with a high concentration of the analyte, you know, say 95 percent or so, well, you simply can't get 115 percent of target, okay, because you required more than 100--you know, more

than the pure material. And that's a situation guidelines simply don't deal with and would be physically impossible to meet. And there are probably a couple of other things that I'm not aware of that could fall into the same category there.

So, certainly the guidelines need to be updated to cover these kinds of cases and probably some others, too.

DR. TIMMERMANS: I was going to make the exact same point that Howard did, and Gary and the NIRVWOG group have gone through the exact same exercise when we were trying to update USP 1119 for NIR methods. I think there should be some type of disclaimer that allows use of scientific rationale for not necessarily addressing all analytical process--I'm sorry, analytical method validation parameters for a process analytical technology.

Exactly, Howard gave one example, I think it also applies to some of the parameters that are currently being addressed in analytical method validation, and I think that that should be realized.

MR. LEIPER: I think that that point is very well made, but I don't know if you've seen

Janet Woodcock's presentation where she actually speaks about CGMP being empirically based just now and she would prefer to see it scientifically based. She also makes a very astute comment on ICH standards, which are--she says that they're consensus-based standards, i.e., they're not scientifically based.

So, you know I think that there's no doubt that people in the agency have got some measure, I think, Joe, of some of the problems that exist in these areas. But we've got to recognize that the industry had the responsibility for putting them there.

MR. FAMULARE: You know, in terms of the basis for GMPs or things that are in ICH, you know, we recognize that the GMPs themselves say that specifications need to be scientifically sound, et cetera. So, I think that, you know, you have to take the references there in context in terms of much of the GMPs are also written about basic common-sense procedural issues, and I think what Janet is saying there is that I think we focus on those issues a lot, you know, whether we have the second signature on the batch record or other procedures in place which may or may not impact

on--and sometimes we may miss the basic science there. So, I think our application very often is empirically and so forth, but, you know, to truly follow GMP, you should have science behind it.

MR. HALE: I'm kind of confused. I think the statements that we need to be science-based are right on, but there's been a lot of--you also hear a lot of complaint about what validation means right now. That we do three lots and call it done; that we do--that there have been years and years of our going over how to test blend samples and all of that. So I don't think validation is perfect as it stands and that this is an opportunity to address the ways that we can approach validation, and some of the comments that have been made that we can take a more statistically viable approach to looking at our processes don't fit into the current way we do validation now. That we do a bunch of work and then we run it three times and then we hang out for a while and collect data or don't collect data.

So, I'm not sure that our--that at least the practice of validation shouldn't change, and this is an opportunity to assess some of those things and to provide a framework to allow the

companies to change the way we do current practice, everywhere from the unit operation side of things where, instead of taking samples, you can look at flow of powders to how we do manufacturing lot release and validation and allow us to learn and all of those things. So, I think the confidence in out current validation approach is not necessarily appropriate.

MR. FAMULARE: You know, I think as the science now is moving on, you know what I'm saying--what does this mean to be science-based--as the science moves on, the C in CGMP changes and that's why GMPs are written in such a broad, flexible way so that--I mean, the hope was when the GMPs were put in place that they wouldn't be constraining on future development. In actual practice, that may not always be the case because there's comfort in knowing that you have this program, this has been acceptable to the agency, this three-lot system. And there's fear in the change.

We talked about that a lot in the prior subcommittee meetings, so I don't think we need to go down that road, but I think just by seeing what's in these slides here this morning that there

is certainly room for improvement in the concept of validation, change in the concept of validation and, you know, even as Ajaz said a lot in the prior subcommittee, the fact that validation, you know, our looking at this, you know, instead of saying blend for 20 minutes, because that's what we validated at, blend to a certain endpoint that your sensor's telling you, you know, we have to make those practical changes, if that's what the science is telling us.

MR. RITCHIE: Joe, that's a good point. Even further, what I imagine is what we're trying to do--the difference between an endpoint measurement that we currently do and release, and a development measurement is to try to say when I have a failure in my development measurement and I have a problem with that batch, more often than not, I still can't determine where that failure came from just because the dissolution failed. But during development, I knew that I made process changes to purposely make my dissolution fail. Now I come along and say, well, during development I have process measurements that I also made when you made your changes to that process, and I think there's some understanding now of why the

dissolution failed.

Is that what we want PAT to do for us? Because right now we can't say what cause and effect is. Do we expect PAT to be both a panacea for industry and the FDA to say, well, we can minimize the number of failures and minimize the number of recalls because now we have an expectation that we've seen the process from the beginning, now to the end?

MR. LEIPER: I think we are expecting--we understand it's processes that deliver consistent quality product. You know, and the pharmaceutical industry is not unique. And that's the way that we probably ought to move forward. And I think that validation is a case in point, but from my experience the problem that we get with the use of new technologies--and I think that you've been--Sonja will bear me out on this--is that we always get the difficult problems to solve. We never actually solve the easy ones.

I guess that what FDA are now looking for is to establish models on the way that we go forward, and I think that the point was made yesterday by Dave Rudd about using suspensions or, indeed, just using liquids and establishing

principles for the way that processes will begin to look, because it's these kinds of systems--and then we can fit all the rest in around it.

MS. SEKULIC: I think it's imperative that we just start looking at our processes. And I keep going back to the method development component of this activity. You know, we've got to start looking at our processes, gathering data in order to translate the data into information and knowledge, to then take that knowledge and accomplish what we're all trying to accomplish, which is better utilization of that knowledge and our processes to eventually--or continue, hopefully, providing the customers with the appropriate quality product. That's really all that it's about. But we've got to start looking. I think that's my point.

MR. CHIBWE: I think one of the things that I expect we can do today is to begin to define in terms of unit operation validation, because if I go back to my job tomorrow and my boss asks me, we're going to implement ABC, how are we going to do it? You were on the subcommittee and working with those guys. How are we going to do the validation?

And really what I want to end up at the end of this day is to confidently say, look, this is where we're going to start working now. Or if we're going to implement the PAT in the batch mode or blending, I think blending is pretty simple. The science is already there, MIT, Purdue, and there are others. There's a lot of scientists already going into that, so I don't think we should hang up on small problems.

What I think we should move on to is the bigger picture in terms of the sample size, specificity, unit operations, and whether within the batch mode or we're going to do the whole unit operation. I could give you examples.

For instance, you could have rejection for content uniformity on-line. You could have LIF telling you that if the potency is below 95 percent, you reject the tablet. So you're going to have to validate that sort of monitoring and control. So I think that's what we should really go into, building on the principles that we've already discussed in the first meeting back in February.

So I think today let's sort of have a path which is going to give us some sort of guidance in

general terms what we're going to do if we decide we're going to implement just the monitoring or monitoring and controlling. So I think those are the things that we should go into.

DR. TIMMERMANS: If I understand correctly, what our discussions have led us to this morning is that that wouldn't be any different than what you're doing now; you know, whether you use a PAT method or whether you use an off-line analytical method, your principles of validation do not change.

MR. CHIBWE: But, you know, what you have to realize is that you're always going to have struggles, especially within the QA departments within the different companies. As long as something looks strange to them, they will tell you they won't accept ABC because ABC is not HPLC anymore. And to them HPLC is primary when it's not.

So what I'm asking for is we should put it down; even if it looks common sense to us, it's not common sense to everybody. So what I'm saying is let's have something that we could work on, and that's actually going to take us forward in terms of--I mean, we don't want to--if we say what we

have now is fine, then maybe we don't need to have the meeting to discuss validation.

DR. C. ANDERSON: I'd like to come back to--oh, I'm sorry. I was actually going to come back to Moheb's point precisely. If we include in this document that existing validation guidelines are adequate for process analytical technologies, we've answered your question. You have something on a document that says the way we validate things now is adequate, QA can see that, that makes your argument for you that it should be acceptable.

MR. CHIBWE: There are always going to be exceptions. We can't use everything that we currently know about validation for the new technologies. Some of the things that we currently use for validation are not applicable to the new technologies. Those are the things I want us to get into so that when we let down--especially, for instance, if I come to the statistical approach and using the rejection, if you're going to be controlling the system, you're going to reject. On what basis are you going to do that rejection?

DR. C. ANDERSON: I agree with you that there are exceptions, but I don't think it's this group's charge to list or prescribe action based on

those exceptions. I think it's this group's charge--and I'm speaking for myself--to come up with general guidances and leave it to the scientists to make correct choices within those general guidances, is my perspective.

DR. NASR: I totally agree with Carl. I think the focus of this group and the assignment we have before us today is to come up with a general guidance, not to go to the specifics for every application and exception and limitation. That should be left to the scientists based on the particular application, and if it is science-based, it will be accepted by the agency.

MR. CHIBWE: What I'm asking for really is not specifics per se. What I'm asking for is principles in which you're going to operate. If you're going to do a unit--for instance, you're going to do a unit validation, how are you going to do the unit validation? Those are some of the principles I think we can get into, without necessarily being specific. But at least you could say this is what you're going to do, you're going to do at least--if the batch size is so large or whatever, but at least have some science-based principle that we should be using.

I don't know. I hope I'm not confusing everybody.

MR. LEIPER: Just a clarification here. When you say "unit," you know, when you're using "unit," what do you--

MR. CHIBWE: Unit operation.

MR. LEIPER: A unit operation, a unit process operation.

MR. CHIBWE: Part of the--yeah.

MR. LEIPER: Okay. I think that, you know, as I said earlier, the thing that's changed, the only thing that's changed from the discussions that we've heard is that we understand the need that we were addressing and have been addressing for the past ten years is not the real need. No, that's the significant change. The way that you would go about it is actually very, you know, quite similar. But we don't break things down into unit operations normally, and we don't do risk assessment or variability assessment. So that would be a change, but that's purely a structural--you know, that's an application of a system if it was seen as being appropriate to go forward. But we need systems to actually allow us to do that.

But that's not going to help you with your guys if they want to do HPLC because they don't understand the need. You know, they're going to solve--they're going to try and solve your company's problem in terms of the technology that they know and love irrespective of how inappropriate that might be. That's something that they go and see a shrink about. That's not a scientist.

[Laughter.]

MR. CHIBWE: Some of it actually goes to their education. The education--

DR. KIBBE: I think, though, that the point that we're talking about right now is how do we transfer what we think we have figured out to people who haven't heard the discussion and haven't bought into the process. And I think it might be useful--I don't know whether we want to do it here, but it might be useful for the agency to pick an example of a technology that is used in this way and say for that technology this might be an appropriate way of validating that technology in this position. And the reason I say that is because if it is so different, the data we're collecting is so large, the data set is so large,

and we're not making point determinations but continuous determinations and we're looking at fingerprints of output, then that example, although not the guidance itself or the guideline, gives people food for thought and a way to understand the general principles of validation which apply regardless of how or what data you're collecting or what endpoints or what measurements you're using to keep track of your process.

Anybody? Go ahead.

MS. SEKULIC: Yes, I tend to agree. I think in keeping with the three-point strategy that Moheb referred to earlier, I think the first one that he cited was validation being tied to a suitable intended-purpose statement was one portion that he wanted to see; the second was sort of length of validation principles in which my opinion is that that really should state something like, you know, current cGMP validation principles should be utilized, you know, when and if applicable for intended use; and then the third component that he had was the sort of citations and, you know, pointing to other sources of information, which is where I think this sort of guidance or documents providing the examples of possible or likely

scenarios might be included.

I'm just going to add that the biggest concessions that I think I've seen in all the discussions fall into two categories for me. One is the sort of encouragement or comment that could be included in the guidance--and we discussed this last time--regarding encouraging industry to have a technology in development, you know, a sort of special category which will alleviate the phobia of actually, you know, trying something on your processes, but not necessarily having to make a release decision on it. I think that's a big concession that industry will see, and I'd really encourage some commentary to that be included into the overarching guidance.

The other big concession that I recall from our discussions last time was the discussion regarding the increased level of scrutiny that some of these technologies may impart on our processes and how to handle that, and we had discussed it at length, the out-of-trend sort of investigation and learning from that as opposed to automatically branding a deviant result as an out-of-specification result, which carries with it its own burdens and paperwork and investigations and so on

and so forth.

So, for me, looking at it, you know, at a higher level generally, not specific to any technique, not specific to any unit operation, those are the big things that I think will encourage industry to sort of, you know, start going down this path and, if possible, to incorporate some general statements on those two points in the guidance I think would be really helpful.

DR. KIBBE: So what you're suggesting is that the agency still sticks with its out-of-specification requirement for investigation, but if there's an out-of-trend, that's something internal and the agency shouldn't get involved with it? Is that--

MS. SEKULIC: Yes.

DR. KIBBE: Okay. Does everybody--okay? You see the subtle difference there? As long as the product is still in specifications but there's a trend that's been picked up by a new methodology, that's not subject to the same kind of regulatory oversight as an out-of-spec would be. I think we talked about that yesterday in generalities, and that's another specification.

Would you want that in a validation guidance document?

MS. SEKULIC: I think it's going to allay some fears in the industry and move us in the right direction. I don't know. I'm open to other people's opinions, but I think it would encourage folks to actually start using this technology.

MR. MADSEN: Let me just make a comment. I think we can't lose sight of the whole concept of control and a state of control in terms of a process. For example, if we had a validated analytical method for the active ingredient content of finished tablets coming off a press where we could on the fly catch--analyzed every one of them and reject with perfect accuracy the ones that were out of specification, let's say normally when we ran this process we found that we were rejecting 1 percent of the tablets, either super-potent or sub-potent, and this was typical, and one day we run this and we find out we're rejecting 30 percent of the tablets, there's still--all of the tablets in good bucket are good tablets, but we've all of a sudden rejected 30 percent of the tablets, which is different than the normal 1 percent.

Now, if I were a regulator, I would be

concerned, even though the product that we're releasing is still good product. And I think somehow we have to make sure that we don't lose sight of this concept of state of control of the process.

MS. SEKULIC: Yes, but, interestingly, you used the word "out of specification." And if it does go out of specification, I think that we would all investigate. What we're talking about is if my process and all the tablets I'm looking at coming out of a tableting run are 98 to 102, but my spec is 85 to 115, there's a lot of room there that I haven't seen with my sensor capability. And so that increased level of scrutiny that I now have will tell me that I'm going out of my normal variability range of 98 to 102. And what happens between 85 and 98 and 102 and 115, that's a learning exercise that I'm venturing to guess the FDA may not necessarily want to be notified that it's happening, but it is important for me to understand my process, to improve my process efficiency.

MR. FAMULARE: I think that's exactly the way the FDA looks at it now. If you look at the current draft guidance that's out there on handling

out-of-specification lab results, I think right in the beginning of it there's one sentence that states that if you have out-of-trend results, if you want to use this guidance internally in the company to examine those, feel free to use it.

But it's certainly, in a different regulatory scrutiny, it's certainly useful information to the company to maybe mitigate or prevent something that may happen in the future.

DR. KIBBE: Anybody else? Go ahead.

DR. MILLER: Just a quick comment. Certainly if all of a sudden the process was rejecting 30 percent of the tablets, it seems to me the company certainly would want to know about that and take corrective action immediately.

[Pause.]

DR. KIBBE: Have we reached a lull? You think maybe w all need a coffee break? It certainly looks like we need an infusion of my drug of choice, so why don't we--we're scheduled for a break, a 15-minute break at 10 o'clock. We'll take it now. We'll come back and maybe during the coffee you'll start to chit-chat and get courage and want to go back and redo this whole thing.

[Recess.]

DR. KIBBE: It would be very useful for all of us to listen to AstraZeneca and how they went about validating a PAT system for one of their products. I think it might be useful for those of us who are worried about how we're going to get started back at the shop to see it actually work somewhere and can be done and to ask some questions about that.

After that, what I would like to do is refer back to Ajaz's presentation on the very first day and the list of questions on the back of that presentation to make sure that we've addressed all the things that we need to address. After that, any other comments or questions or what have you from any of you would be well placed, and then I think we'll probably let you break, and it probably will happen earlier than our time frame. And I will sit with the stuff that we've put together and come up with a handful of slides for this afternoon's presentation to the full group.

Now that everybody has gotten a chance to kind of relax and get back in the mood for serious thoughts about PAT, we have AstraZeneca up from the floor, with overheads, no doubt. Overheads, Bob? Thanks. Overheads. Outstanding. Can

we--wonderful. Technology is wonderful, isn't it, folks?

This is the application of older technology to the understanding of future technology. And remember, folks, that the technology that's most important is the technology you carry around inside your head, and that's been with us for millions of years.

MR. CHISHOLM: I'll keep this down to certainly less than ten minutes, but please ask any questions. I'm sure--I think Ali has come in, has he? Ali will be in, and Ken, also.

I like to put this up because I've been seeing it for the past two days now, and when it comes to what we're talking about, it's an essentially very important thing. "Statistical thinking will one day be as necessary for efficient citizenship as the ability to read and write," and that was H.G. Wells in 1925. And that's essentially what we're talking about here to a large extent.

What I wanted to talk about is a plant that we sanctioned and built in Germany and it's an important tablet facility. It's a very straightforward plant, solid dosage, therefore,

you're talking a dispensary, and you've got two routes. You can either go dry granulation or wet granulation. If you go wet granulation, you go through a collect granulator and a fluid bed dryer. If you go direct compression, you don't go through a collect granulator and a fluid bed dryer. You go straight to blending, and then from blending into the tablet press.

I've put up the network diagram, not to alarm you but just to try and broaden the discussion, because what I think the discussion is seen to have done this morning is very much a view of an isolated system like a sensor, and these systems aren't isolated. If you're going to actually do this as a total solution, you've got to look at it holistically. And, really, you're talking about such things happening from cradle to grave throughout your plant.

If you look here, you'll see--I'm going to have to walk across, so I'll shout in my Scottish voice. Can everybody hear me?

Spectrometers here--

VOICES: Can't hear you.

[Pause.]

MR. CHISHOLM: Can everybody hear me now?

Okay.

You see there are four spectrometers here for the solid dosage plant. The first one is basically monitoring everything that goes into the dispensaries, and also it's multiplexed so it's also controlling the fluid bed dryer. The second one is an especially developed one which mounts on an IBC on the blender, and then we have them also exit the tablet presses.

So everything coming in is checked. The blend is actually controlled to a blend endpoint which will be variable time depending on the formulation. And that's quality, if you like, control of what we're doing. It's actually a statistical process monitoring, if the truth be told.

Once you get to the tablet press, we're statistically monitoring tablets coming off, and that's your quality assurance. So you've got to think of the two as being different. Really, actually make it operate, as we have a final PC. This is all 21 C.F.R. 11, so this is password-controlled. It talks to a server, which is up here. Server calls in the analyzer. The operator then bar codes the product he's going to

look at, fits in the probe and gets the reading back.

That's just simple and that's the sort of things that we do just now. But as you can see, for an application like this we've actually ethernetted the whole thing, and that's the NIR server controls everything, because we've taken a completely holistic view of the plant.

You could actually talk to the system from anywhere in AstraZeneca if you knew the right way to get into it, because it's on the ethernet up here, and it's also connected up to the company network. Okay?

So that in itself brings in a lot of validation worries because you have what's essentially an open system, and 21 C.F.R. 11 doesn't like open systems. So there are issues there that we have to get concerned about.

So you can see how that works. So throughout the batch, actually monitoring everyone going through the dispensaries, controlling the dryer, controlling the blend to endpoint, and then statistically monitoring tablet presses for things like active content, et cetera, et cetera, et cetera. Okay?

And that's not that much different really, I don't suppose, from what we do just now, except they keep using the word "statistically monitoring," because you do it throughout the batch, and we do it for every critical variable that we see there.

The thing you have to really start to worry about is how to handle the data sets you're going to get because these data sets are very, very big. If you think that of a product life, let's say, 20 years, and you may have to keep that data for regulatory purposes or whatever for 20 years, that's not been defined, and I think perhaps the guideline needs to start thinking about defining things like that. Then you've got a big job on your hands and you're into archiving.

If we look at it, the sort of things you need, the diagram I've just shown you is something like that there and that there, because that's the operational part in the plant. And that's the NIR server, which is the brains of the system, and down here you've got a number of analyzers with their associated controls, et cetera.

So let's try and think how this works. People have been talking about having to go back

and implement something like this. Well, let's say that we take a tablet and we want to do the active content. Well, the first thing you've got to do in any of these things is this system's dumb, it's silly. You've got to create a model because it doesn't know what it's doing. So you take a tablet through an analyzer; the analyzer will analyze it, send a spectral up, and it will be stored here. So you've got to have spectral data and model version storage. You've got to have--these are module--these are functionalities. They're not necessarily separate computers. You've got to have some way in the long term of storing all the spectral.

So you've done that with your tablet. You've still got it because the nice thing about these techniques is they're non-destructive. So you want to go across, you stick it in your HPLC, it tells you the active content, and then it goes into the analytical data storage module.

Now, validation terms is a very critical issue here. If this says Batch A, Tablet 17, then that's got to say Batch A, Tablet 17, and these aren't simple issues. Because one day a regulator is going to come across and say tell me what

happened to Batch A, Tablet 17. So all that data has to be stored, and basically it's got to be traceable. You then--and Sonja and Ali know an awful lot more about this than I do. This will go into some sort of kilometric modeling module, back down here, and gradually you would create your algorithm, which is your model.

Now, actually you've now done your modeling, and I would say to you from a validation viewpoint you need to continue to store all that modeling data, because one day someone from the agency will come along and say, How did you create the algorithm?

So there are a lot of problems in information storage and retrieval here, and we haven't really addressed any of these in what we've been saying. Whether or not it should appear in general data in any way, I don't know. It's up to you. But it's a lot more complicated than people think it is.

You've got your model there, nicely stored up here. So you've then got to validate your model. Notice I'm using the word "validate the model." Now, how do you do that? Well, you carry on and do the same thing as before. Tablets that

are here, don't let them be destroyed. Stick them through there. And what's happening this time is spectral are coming up, the system is predicting, it's telling you what the active content is. You take it, HPLC it, that comes out here, and it tells you what the active content actually is.

That's a way of validating, isn't it? Because you're now relating your spectra and your model to actual data on the plant through registered process test the way we would have done it before. And in the initial stages of all these things, I cannot see any way to move away from the accepted test. That's why I said yesterday you've got to learn to walk before you can run.

We will have to base it on our old methodologies just to model and then to validate the model.

So you've now validated your model, and you're going to normal production. All that's happening is the tablets are coming through, statistically through the batch, not every tablet, because there's far too many, and you need lots of analyzers if you're going to do every tablet, and there's no need.

It comes up here. It says predict and

tells you the result, and you release a tablet based on that result because you've got a validated model and a validated process. Okay? Is everybody happy with that?

MR. HALE: Bob, when you say you release a tablet, do you actually release a tablet or do you release a batch?

MR. CHISHOLM: That's a question to throw open to everybody. Clearly, you would take the results across a batch. You give me an immediate problem there, because if you find a tablet is now what you'd like it to be, you have to be able to identify that tablet given the data that are coming off the tablet press. This plant is just in the process as we speak of being validated, so we haven't practically released anything yet. So you've given me food for thought, which is what these occasions are all about. Yes, we've got to take these decisions.

Okay. So you've got your spectral data storage. You've got your servers and your analyzers. You've got your modeling module here, analytical data storage. You've got traceability for the inspector who comes in a few years later. You can show how you built your model, how you made

the algorithm, how you validated it. So you've got to have something here that actually stores all these reports because you're going to have to have validation report for that stage, and you're going to have to have batch reports or functionality of reporting is required down here, again, long-term storage.

But there's something else I think you need, and the lady yesterday asked about control. What I've put down here is an HPE module and I started trending, manufacturing execution. To get the best out of these systems and improve your knowledge, what you're actually doing as you go through the batch is statistically process monitoring, just to make sure the trends aren't beginning to take you out of compliance. And you'll have alarm levels or, call them what you will, warning levels. And you'll watch that in the normal batch.

But over a period of time, you will have built up a history of a large number of batches, and you want to store that data because you want to data mine it; therefore, by data mining you can see when your process changed slightly, you begin to understand why it changed.

And I've heard one or two questions this morning about would, for instance, just doing end testing be sufficient? Well, for me the answer is no because I think you need to take a total approach to control. I would say that I'm control engineer.

One thing I've learned throughout my career at AZI, et cetera, is that things always change. Manufacturing processes always change. Materials always change. That's just a basic given. So you've really got to take that into account, and that's why we're trying to take a total approach to this.

Okay. Any questions? Does that help anybody? Is that you, Ali? I can't see that far back.

MR. AFNAN: The question that was asked of do you release the batch based on that tablet, I think another question is, yes, we would release a batch based on a statistically representative number of tablets which have been analyzed. Now, if you have a batch of two million, the question I have--and I don't have the answer--is: What is a statistically representative sample?

Now, let's say if you said it's 1 percent,

out of 200,000 that's 2,000 tablets. Now, of the 2,000 tablets, considering that our processes are based on the way we've been manufacturing until now, if we did 2,000 tablets out of a batch, I have no idea, but I would be surprised if all 2,000 were within spec, whatever that spec is.

So then what do you do with the numbers that fall out of spec, and I think that was answered yesterday where you would see things which are out of your window of operation, window of acceptability. And that's a completely different new ball game. But there will be those that come because if you go from 6 to 2,000, you're going to see things you've never seen before.

So the answer is we probably would release the batch, but you would have to see what that change was, because at the same time we're no longer going to come up with an answer which says the tablet is good or the tablet is bad, but you actually say, well, yeah, you find that the solution was wrong but all the other aspects of it were right, because, again, we're not just looking at one property of one component of your product. We're looking at the full process. So it doesn't matter if one part of it is--well, "doesn't matter"

is the wrong terminology. But you're looking at a complete picture rather than just one tiny part of it.

DR. KIBBE: Tom?

MR. HALE: I think it comes--in the context of validation, I think as information is gathered and experience is gained, one thing that will come up is the definition of a batch, because a compressing machine can be looked at as a continuous process. And as described here, it's a whole bunch of tablets coming off in a row, and it really is a continuous process.

As this advances and the opportunities are increased and knowledge is gained and people learn, I think what will be challenged is this idea of batch size, of what that really means. We artificially describe it somehow, but I think that especially in a guidance point of view, as these things evolve, we need to have the opportunity to address that issue both in terms of how--as was stated, the sample size, how we deal with samples, how we deal with them statistically, and how we deal with them from a batch size and validation point of view, and that the whole concept in the context of what Bob was saying of a holistic

approach needs to be written into this guidance, I believe.

DR. KIBBE: Does it need to be into the validation guidance, or do we need to understand it in other ways? The possibility is that they will have process measurements or assessments that apply to every tablet as they come off the line. Now, that might be down the road, but it's a possibility. And then your question--do you release that tablet or do you release the batch?--really will go down to the fact that we release every tablet that fits and we throw every tablet out that doesn't. And when we start throwing out a lot of tablets, then we start relooking at our whole process. And in that case, batch becomes meaningless, and process control is everything. And that changes a lot of the way the end user looks at things, which is the physician and the patient.

And so there's a lot of---do you want to respond? I saw your hand come up. You have to talk into the mike, though.

MR. AFNAN: Okay. There is another side to this. We have a way of looking at the way we have been operating until now, which is you go in

in the morning and you do nothing until the afternoon. In the afternoon, you look at the quality of your tablet.

Now, if you've actually been controlling--and I use the word there "controlling." I know a lot of people have difficulty with the word "control," but controlling your processes, then when you come to look at your tablets, all you're doing, you're assuring the quality. You're not controlling the quality. Because once it's a tablet, it's too late. If it's a bad product, it's a bad product. If it's good product, it's a good product.

What you should be doing--and I think that's what PAT is--make sure you make a good tablet. So then the whole concept becomes different by saying, well, let's not just look at the tablet. You have to look at the whole process. If you've looked at your process and you have been in control of your individual steps, then it's only really a final check. You know, when you make coffee, you pour coffee into the cup or into the jar. Well, in Europe we pour it into the cup, and you pour hot water on it. You don't stick it in your mouth to see whether it burns or not. You

know it's hot. It will burn.

So it's the whole concept that you should look at the full process rather than, let's say, well, how many tablets do we release or how many do we reject? I don't think we're capable of doing the whole number of tablets which are being manufactured. That will not fly. And I don't think that would actually--you know, at the rate of 200,000 an hour coming out, there's too many tablets coming out in a given minute for us to control every one of those and say, well, we reject this one, we reject the other one. The whole concept is you shouldn't have any bad tablets rather than let's see which is bad and which is good. You shouldn't have any bad tablets. We're just confirming that we don't have any bad tablets.

DR. KIBBE: Anybody else?

[No response.]

MR. CHISHOLM: I'll finish off with this quotation and maybe to show you how difficult it is. It's called "The Impact of Innovation." "There is nothing more difficult to plan, more doubtful of success, nor more dangerous to manage than the creation of a new system. For the initiator has the enmity of all who would profit by

the preservation of the old institutions, and merely lukewarm defenders and those who should gain by the new ones." That was Machiavelli in 1527, and I guess it applies to what we're doing today, because it's very difficult to get these things accepted inside your own companies.

Okay. No more questions?

MR. CHIBWE: I just had one question for you, Bob. Is the system optimized? And did you validate it?

MR. CHISHOLM: The system is being validated at the moment. The system is running. But the plant has only just started up. It's a new plant.

MR. CHIBWE: Did you have some sort of guideline to follow your validation, your--

MR. CHISHOLM: No, we--would you like me to talk a little bit about that? We had to invent our own.

MR. AFNAN: Logic.

[Laughter.]

MR. CHISHOLM: I'll talk a little bit about it. This is an existing product, which is a good one to start with. We have five years' worth of production experience, therefore, five years'

worth of retained samples. So we have been creating a model using these retained samples to start with to get us going. So that's where the model is coming from to get us off.

Having done that, now we're starting the plants us, and we'll have this whole system running, and we'll be able to expand the model through the additional data. And that will change because whenever any new plant and things change, that's something you have to recognize. So you have to expand your model and make it more relevant. That's the stage we're at just now.

We're also making designer, for want of a better words, tablets because this is a very well controlled product and we want to broaden this across the specification range, which is another difficult thing. But you'll find if you have a very well controlled process, it's far better if your process was a bit of a mess because you get more data quicker.

So that's the stages we're going through. The actual validation of what we would intend to do is something like along the lines that I've described. Because it's an existing product, we would run traditional registered methods which are

registered for this product, and also run the NIR and compile parallel dossiers to demonstrate equivalence between the two methods for a period of time we'd have to talk to the agency about. These are all new areas, and they're also difficult, I think, at this point in time to put in a gate because I don't think we necessarily know the answers. But I think the answer to that is that's something you've got to discuss, and you've got to try and make it statistically relevant, so we've got a statistician who is involved in experimental design of this and who will give us advice on these things.

MR. CHIBWE: Are there any lessons learned that you could probably share with us? I mean, you don't have to share any proprietary information, but just some lessons. I mean, as you go through a process, of course, you're going to go through certain things. I'm just wondering if there's things here in the U.S. that we could probably learn from you in terms of putting up the validation principles.

MR. CHISHOLM: I think maybe the lesson learned that I don't think we've been as good at as we should have been is you have to have a

cross-functional team approach to this. It's not just Ali Afnan and Bob Chisholm. It's got to be the people in plants. It's got to involve pharmacists as well. It's got to involve QA people. We've now got a full-time QA person, and that's who's going to compile the dossier.

It's all about teamwork at the end of the day. The original concepts were Ali's, (?) , and mine. We did the original strategy. We actually ourselves sat down with Jim Drennen and brainstormed how we could do this, and we developed micromodel 1, micromodel 2, moving into micromodel in the plant with validation at each stage.

But all this, this is becoming accepted and the sort of normal vocabulary, but this is so new, you're doing it for the first time. And there's just nothing in the literature about it. So teamwork is very important or you won't succeed.

MR. CHIBWE: Just one last question. Are you doing cross-validation for all the critical pieces or just certain selected parts of the process?

MR. CHISHOLM: No, this is a new plant. This plant has been totally validated. What I'm describing is just the validation of the associated

process analytical technology and our achievements. The plant itself has gone through all the normal validation you would expect: equipment validation, et cetera, performance qualification. Yeah, it's gone through all of that, and it's been done using existing methodologies and using existing registered tests because it's an existing product. It's a new facility but an existing product. That's why I tried to let people see there is a distinction to be drawn.

MR. CHIBWE: Thanks.

MR. CHISHOLM: Okay. Everybody happy?

DR. KIBBE: You have a question?

MR. RITCHIE: When you go live, will there be--I mean, I see an opportunity here for this to be a textbook model, if you will, on how the rest of the industry should proceed. When do you perceive that happening or becoming information in terms of a book or something?

MR. CHISHOLM: I've got no problem with that, to be honest, but there are others who would have a problem with it. It's my belief that FDA, MCA want the industry to move forward as an industry, and we'll get there quicker if we all move forward together. So I have no problem in

information sharing.

I certainly would not be doing that sort of thing until we actually had made a submission, I don't think. That would seem reasonable because that's a very important part of it. And there may be a lot to learn from that. But it would be then up to my regulators and the others to decide whether or not we published everything or what was intellectual property. That would not just be my decision in isolation. But I totally agree with what you're asking.

DR. KIBBE: Okay? Well, thank you very much. From Machiavelli to H.G. Wells to 2002 and process and you.

One of the things that we've been asked to do is take a look at the method of validation issues that were listed on the back of Ajaz's handout that went with his first presentation earlier on. For those of you who have them, I think we can go through them in a reasonably expeditious system. Our support people here have been gracious enough to also put them on slides so that we can read them if you don't have them in front of you.

MR. HALE: Could I jump in before you

start that to follow up on Bob's talk, that one thing we might want to think of in terms of our guiding principles for validation, or whatever that list was that we came up with, is that there is a need and a desire that if PATs lead to the introductions of new approaches for process control, that there will be a mechanism to work with the FDA to institute those new methodologies. I think it's critical to keep that door open, that as these technologies allow changes that are more fundamental than just sensors, that there is a mechanism and a desire to work with the industry to make that happen, as in the case of AstraZeneca. And it has to be a guiding principle, I think.

DR. KIBBE: Okay. Anybody else?

[No response.]

DR. KIBBE: All right. Tom? It's our last presentation slide, I think basically.

[Pause.]

DR. KIBBE: Okay, while they're typing, I hope everyone has got a copy of Ajaz's presentation. We could start with the first statement, which will also be put up there when they get caught up with us. It says that a validated laboratory method exists for regulatory

parameter across NDA range. How do we replace this with a PAT method? Is there anyone who wants to comment on that?

DR. TIMMERMANS: Art, before we get into that, let me just put a little bit--not necessarily a disclaimer, but what Ajaz--what we're looking at right now is a number of discussion points that we went over when Ajaz came to Merck fairly recently. It's certainly not an all-encompassing list of what we see are necessarily issues, but it's just a couple of highlights that were plucked out and, you know, the answers that are written up here with some of the outcome of the discussion. But, again, that was done among a very small group of people with Ajaz and Chris Cole from the FDA guiding us. So just so people are aware and put this in the right context.

DR. KIBBE: Okay. We now have context. This is questions and responses that came from a discussion between FDA staff and members of one of the larger pharmaceutical firms--in beautiful downtown southeast Pennsylvania and at West Point?

DR. TIMMERMANS: Central New Jersey.

DR. KIBBE: Oh, interlopers. Okay. So regardless of where the item came from, what do we

think?

We don't think? We do think? Jerry?

DR. WORKMAN: Is there any relevance between this discussion and the slides? I don't think so right now, right? The slides have nothing to do with this; is that correct?

DR. KIBBE: It should.

DR. WORKMAN: Oh, there we go. Sorry.

DR. KIBBE: These slides are these statements, I hope. Okay?

DR. WORKMAN: Sorry. Thank you.

DR. KIBBE: What I read I think is their number two. I was just using this paper as a--you know. I don't care. We can go anywhere.

T3A This is a regulatory parameter across an NDA range, and that's the first item under the PAT method of validation issues on the handout. Right? It's listed number two up there, but don't let that confuse you too much.

So the question is: Do we have any thoughts on these items? And we'll put them up one at a time, and if there are thoughts, then we'll try to see if that is needed to be reflected in what we've already produced. Have I got everybody completely and thoroughly confused? It's my role

as an instructor to confuse the students so that when they take the exam, they don't do well. Because, otherwise, how can I flunk them out?

DR. WORKMAN: Excuse me. Does this involve correlating the new method to the old method? It's a question for the group.

DR. C. ANDERSON: I would take it as a given that it does. Further, in the answer to that example, we need to include some sort of statement that specifies that the PAT may or may not span the range of the original validated method, and that's acceptable.

DR. KIBBE: It also can go the other way, too. The PAT might actually have information that goes further than the validated method.

DR. WORKMAN: It may be implicit in this, but do you want to make it explicit that when you validate the PAT method that it does correlate with the original validated method?

DR. KIBBE: So we want to add to the second paragraph here that the methods are correlated and they don't necessarily cover the same range of information? And that's still acceptable?

How's my man doing over there?

[Inaudible comments off microphone.]

DR. KIBBE: Sure. That works. Italics, yes. There's a program called Edit that, when you--I always push "edit" on my word processor, and then when I start changing things, you have to accept or reject the edits. I don't have to worry about changing fonts or crossing-outs and things. It just does it. Horrible to be slaves to all of this equipment. Bring back the quill.

DR. CIURCZAK: There's one thing on this. We want to be careful about correlating it because you may be doing a process method for which there is no method right now. Thickness of coating, on-line, because, you know, I just mean that you have to be careful about correlating it to a method that doesn't exist.

DR. KIBBE: The statement says, assumes that there is one.

DR. CIURCZAK: Assumes, but, I mean, you may be doing more tests. You don't want to have the idea of having more tests, different tests.

DR. KIBBE: We have lots more questions, so this one said--okay. We've got one, we got a new one, what do we do? Well, we do a correlation.

DR. WORKMAN: Excuse me. There was also a

statement about the ranges may not be identical.

DR. KIBBE: Right.

DR. C. ANDERSON: There is actually another example coming up that will address that. I got ahead of the game.

DR. KIBBE: Good man. Okay. So we're happy--yes, sir? We're not happy. You have to push your little button or we can't hear you.

DR. WOLD: The correlate is to me fairly diffuse. If you have a correlation of 0.1, it correlates, but it's not a very good correlation. And I think one needs some statement that it should correlate within the error measurement of the traditional method, or something like that, over the range of interest; otherwise, you are in trouble.

DR. TIMMERMANS: The question is whether it should correlate to the same accuracy as the existing method or should it correlate to the accuracy required by the process or the information that you need?

DR. C. ANDERSON: I think the answer to that is very clearly it has to be suitable for intended use, and the existing method may or may not be more precise than is necessary. So I think