problem, it is on the market. So when you add a new approach, then that--something becomes visible. So it's a different question in a sense. Under the current paradigm, there's no issue at all. So for this--sorry, for this class of problems, quote/quote, "problems," I don't know what whether we should even call them problems because they're not problems. So these are really variability and observations which are not visible under the current system.

DR. MARK: So, it does go deviation handling, Ajaz, and that goes to compliance, that goes to regulatory issues, that goes to, you know, what we were talking about this morning. So, suppose the damn sensor goes off and it goes wacky, okay, so there's 5 minutes or 10 minutes of product that's being redirected into a different stream of product collection. Now, how do we handle that deviation, do we go back and find out that, okay, the sensors off, so we get that fixed, we then do we take the material and put it back through the system or do we test it by the current applicable, approved methodology? These are the nuances--

DR. HUSSAIN: That's a sort of different example. What we're talking about here is, a

company is willing to put PAT on line and go through the validation development process. I think the better example is one which is was supplied to us by G.K. Raju, and it's in Janet Woodcock's presentation. And the example simply is, a company would like to--and it's a real-life example, it is the data that he has supplied--would like to do online blending uniformity analysis. And now, when they are doing this in an R&D efforts they're using the same product, the same condition, but not in the manufacturing setting. They see non-normal distribution or trends which show that the current blending, well, as it's being manufactured, may have some deviations there which are not visible under the current system.

It's also an example that I'll sort of ferret you, as in the sense, due to the PQRI blend uniformity process, a company, which will remain nameless, wanted to do the stratified sampling and get data to support the PQRI proposal. A validated product, on the market, meets U.S. content uniformity, a history of that--even meets the blend sampling analysis, without any problem. So when they did the stratified sampling, they found towards the end of the run, there was a deviation.

That happened. But they did that only to sort of be nice and give some data to PQRI, so are they in trouble now? So they send the data to me, I didn't hide it, I showed it to you guys before--to fix the problem, right, and how. And that's the scenario we're talking about.

MR. FAMULARE: Again, the aim is, you know, there's so much focus on what will happen in compliance, but the aim is to go to product improvement and if the compliance enforcement policy is such that it penalizes you, then we will have defeated our purpose.

DR. BOEHLERT: I was going to point out these things happen now, as Joe says. And, you know, I've run into situations where somebody, in analytical testing, say, has set a limit on impurities of 1 percent and they've been testing it all along and find less than 1 percent. They improve the method and now they find out they have 2 percent. It doesn't meet their filed regulatory specifications, so the question is, has it been there all along?

And the best you can do, very often is infer that it has because you haven't changed the process and you haven't done a lot of things, but

you can't go back and reanalyze samples that are beyond your retain period. So the best--you know, so you might want to talk about an approach on how you might handle those situations but, in fact, people fact it all the time right now.

DR. HUSSAIN: I think that's a very good example. And maybe--let me try to answer that question, maybe that'll help the committee.

The current testing paradigm that we have and so--which is the sort of limited testing and release, so we don't have--we have data which is very limited. A company wishing to do PAT on line my say, all right, we are going to establish a baseline which would be, collect all the information, the history of that product and so forth, and have that available, too, for discussion because that becomes a baseline for that product already. And that any deviations that are apparent under the new system are either corrected or not corrected depending on if it should be corrected or not.

But then the reference point is the baseline data. That maybe a bit more data that they need collect.

DR. MORRIS: Can I ask a question then?

And maybe it's for both you and Joe, Ajaz, but 4c, then, is sort of a question that differentiates the way we are currently handling, say, out of trend data that are not part of the manufacturing process compliance testing now, versus how we would handle it during PAT implementation. Is that a fair assessment?

DR. HUSSAIN: In my mind, it is, because, in my mind, you're trying to create a whole new team for review as an inspector. And in some ways a new process for handling all these issues--

DR. MORRIS: Right, I mean, because--

DR. HUSSAIN: --I mean, hopefully, a better, more efficient approach, so.

DR. MORRIS: I would just say that the idea of a safe harbor doesn't, I mean, what you're describing, Joe, is sort of what's done now anyway. And all I'm saying is that if you have foresee implemented somehow that does differentiate in terms of extending the harbor, if you will.

MR. FAMULARE: That's true in the sense that, as Ajaz, started out before. It is a new paradigm, you know, all we have now is based on the conventional methods of analysis. So it is a new paradigm because you're voluntarily introducing a

new factor towards product improvement. So it would change--that's why, as Ajaz says, we have the team approach, training that we're going to be talking about, et cetera, and ways to deal with that new paradigm.

DR. SHEK: Yes, if we go back to the specific question whether a priori we should have some guidelines. I just listened to the discussion, in real life, I don't know whether that will be practical until you don't go right and do the test. And the scenario's a little bit different today. We are changing, let's say, the sensitivity, okay, of the tool that is in our hand now. So by definition, we are going to see things that we haven't seen before. Then you have to go and ask the question what does it mean, right, whatever we call it--is it important or it's not important? And that's going to be based on case-by-case. So the best approach would be, of course, we are taking the understanding could be both from the regulatory, you know, agencies, as well as from the manufacturer. It has to be case-by-case and understanding what's really is happening there. Today, we establish specification based on analytical tools that are in our hands and

based on the process capabilities. And we might come to a situation where the PAT will indicate to us that you should go some direction, and maybe the process would enable you to reach there. This thing happened over and over again in analytical, right? We developed sensitive, you know, perfect separation, but we didn't have a detector who can pick out those differences. Then we came out with super detectors who were able to now, improve on the columns.

The same thing might happen here, but it might take, maybe, a little bit longer. So the most important thing is to have this dialogue going on and understanding what PAT is doing and what we are observing there, but to come out with a priori rules, I think it will be difficult.

DR. HUSSAIN: With respect to sort of impurities, in the sense, in one sense because of its presence all along, it's qualified on that basis, I mean, so that would be the approach.

So in some cases, the availability of whatever flaw we see, would that be qualified on the basis of historical presence. And that would be one approach.

So there wouldn't be any issue remaining

at all.

DR. KIBBE: Just--I'm having a hard time imagining these disasters, which--but I'm going to work my way through it. If we put a new way of monitoring a process in place and because we are ethical manufacturers we want to always improve our process and we suddenly find that a certain portion of our batch is always out of compliance. Okay? Now, what does that mean to the end user? And, as a company, first, you're--you should be overjoyed that you found this problem, because you now will then be able to not disadvantage your end user, okay? And finding it, whether we use PAT or we do something else or somebody else finds it for you, it still has to be remedied.

My personal opinion is, however, that what you will find are things about your process that really don't disadvantage the end user. You'll find things out that are within the general scope of what we've used as a way of clearing each batch already. And any change or any variation which does not exceed the batch requirements that we already have in place, are yours to deal with and not the regulatory agencies to deal with. They're not going to say you have to throw that batch out

because you have some variation within it that's still within the framework of how you get the batch approved.

And if we do find that the last 600 tablets of every batch you ever made are junk and should be canned. Then we're going to ask you to fix that because we don't want you to keep sending out those 600 tablets. And you don't want to do it either, all right?

So I think--

DR. MORRIS: I think that's the easier case, though, Art, I mean, I don't anybody's arguing that. I think the question and--on the table, really deals more with paving the way for companies to try. If they don't want to have to trigger and OOS investigation if it's one of the variations that you're talking about that doesn't effect the end product.

DR. KIBBE: And that's what I'm saying, if it doesn't affect the product then that's where we draw the line.

DR. MORRIS: I mean, I can't speak for Ajaz here.

DR. KIBBE: You don't have to do anything else. If you find a variation and it doesn't

affect the quality of the product, vis-a-vis the standards that you've already established for an ongoing product, the agency isn't going to make you do anything outstanding.

DR. MORRIS: Well, then, maybe that's the a priori criteria then.

DR. KIBBE: All right, and then if there is an impact on the patient, you better do something because once we find out, we want you to do something.

DR. HUSSAIN: In that regard, I think the proposal to--sort of the definition of safe harbor covered that and you'll not need anymore things, okay.

DR. LAYLOFF: I guess--did you want to--

MR. HALE: Yeah, just a quick one. The a priori part of this in my mind is if you're going to make an effort to collect more data, what is the purpose of collecting data in the first place? I mean, putting a sensor on for the sake of putting a sensor on, makes absolutely no sense unless you have a plan that you're going to look for something. And it goes back to the idea of development, even if you're in manufacturing there needs to be a purpose up front for doing it. And

if you have a purpose, then that thought process should be played out that you're--that you have a process to react to the data. I mean, putting on for the sake of sensors doesn't make any sense to me without a thought process that goes into it.

DR. MARK: Yeah, it's sort of--a good point, it occurs to me that if you say, okay, we're going to use this to improve our process, you're sort of saying, we're going to use this as a way of telling us when the process is not as satisfactory as it could be, if you will, and that's almost tantamount to defining the process as being unsatisfactory then, which his a danger or a pitfall you might fall into, if you're not careful and it could, you know--you want to make--to improve the process, but you don't want to say, well, the process isn't satisfactory now, because we can improve it.

MR. CHISHOLM: Yeah, I'm just thinking as I do, if I was a man from Mars and landed in this, I'd be listening to an industry that's absolutely scared because it doesn't believe that its existing process isn't good enough. And I think, as an industry, we better be somewhat careful of that. I totally support Arthur across here. We're an

ethical pharmaceutical industry, if we're putting rubbish out there that ain't helping the patients, we want to know about it.

I think the problems you're talking about relate to other things. I think that we will have more trouble with our internal regulators and QA people sticking to your rules than anything else. I mean we'll be simply embargoing and putting into quarantine more and more batches if we're not careful. And that's up to us as an industry, to sort out. We've got to sort out both sides of the fence.

The thing that concerns me is I think we're moving away from yes and no to maybe, which I said, this morning, but I mean, if you try and define that a bit better. But it's when you actually want to control the process. If you are finding something's going slightly wrong at the end of a batch. And I'm quite sure there must be lots of examples of it, through blending, et cetera, et cetera, et cetera. Do you have to throw away the whole batch of which 95 percent might be good. In the currently existing situation, you would. These are the sort of questions I think that we have to address. Because if you're actually monitoring

quality assurance in real time, then you know when it's going wrong. You know what's wrong and what's bad.

And, in fact, if you got to stage in a tablet press towards the end of a batch that was going out of spec, stop the process. So we have to try and think in a different way. I mean, I'm a control engineer by degree, think more along these lines and away from the old yes and no and into the control system philosophy. And we all have to do that, I think. And stop painting this dead lakes scenario I keep hearing.

DR. LAYLOFF: I have a comment. I think we've drifted off a lot into what is possible, rather than to what is probable. I reviewed, not too long ago, the content uniformity data on 10,000 different batches analyzed in one FDA lab in St. Louis and it was quite striking how consistent the products were and how few there were out of limits. I don't think there was a big elephant out there that people are going to trip on. I think what we're going to see is efficiencies in production. I think we'll see a better consistency in product, but I don't think there's an elephant out there that the industry's missed. It's a very good

industry and we've got lots of good product out there and I'd like to move on to the next question. The next question? Yeah, go ahead.

DR. RUDD: Yeah, could I just briefly add one comment? And, actually, to re-enforce what Bob as said. We need to think much more about the positive aspects and not get hung up on the potential ghosts and shadows that are out there to catch us. Can I give one example of where I think we could implementation PATs overnight. We've had debate, already, about, you know, is it a development thing, is it a manufacturing thing? And we all have view on that, but we could implementation the following example overnight for existing products.

And I'll call this a hypothetical situation, although it may ring true with some of us in the industry. Not with GSK, I hasten to add. But imagine a liquid suspension product, where the bulk suspension is being filled into unit containers. We've all had experience of homogeneity issues there, whether it's sedimentation, foaming, flocculation, that sort of thing, such that it's possible that towards the end of the filling run, you may have to discard a

certain amount of the bulk or the fill material because it's subpotent material or superpotent material, it doesn't happen in GSK, but some of us may of products like that.

The current approach that we're using is to play safe, you know, we do some validation studies and we say, okay, the last 10 percent maybe is at risk, so we'll reject and discard the last 20 percent. Kind of rule-of-thumb there, you know, that's the way we solved the problem at the moment. how about, overnight, if we implement a PAT approach, if we put some fiber optic UV, fiber optic approach in there and we continue filing until the point at which we begin to get close to subpotent or superpotent material, that may be 20 percent on some occasions, it may be 10 percent on other occasions. It may be 1 percent on subsequent occasions. So, without investigating the process, without doing any development work, simply by implementing the measurement, what we've achieved is a level of control, the thing that Bob was talking about. And that level of control has improved our process, because now, we're not working within this, you know, belt-and-braces, safety barrier of rejecting, for example, 20

percent every time, we're rejecting the amount that needs to be rejected and probably, routinely, that would be a lot less than 20.

So the point, really, is just to recognize that there are different levels of implementation here and we really shouldn't get hung up on the potential risk and ghosts and shadows. Let's look at the positive bits and let's do those if they're quick and easy to do. Let's do them and let's do them overnight. Thanks.

DR. HUSSAIN: An excellent example, I think, sir.

DR. RUDD: Purely hypothetical and not GSK, exactly.

DR. LAYLOFF: Okay, going on to Question 4d, What other mechanisms do you recommend for consideration? We've pretty much beat that up.

DR. HUSSAIN: Just, I think I want to sort of bring a perspective up. Listening to Bob and David and so forth, I think a lot of these questions we were driven in this direction because every meeting I have been to, every place I have been to is that's the only question, the flaws, the flaws, the flaws. I mean, I'm getting scared here. I totally agree with Bob, in this instance. I

think we need to focus on the quality of this. These questions were. sort of, with that mind set in mind. So.

DR. MORRIS: Just follow up on that, though, I don't think you should be too hard on yourself here, only because not representative of any companies, but GSK and perhaps AstraZeneca, I mean, these are--these may be lower energy barriers for PAT implementation in other companies and it's the companies who aren't already sort of embracing the mentality that you don't want to scare off.

So, I don't, I think it's fine to address them, I think you have to.

DR. LAYLOFF: Okay, let's move on to Question 4e: What are your recommendations for training needs and criteria for certification of the proposed PAT-Team?

DR. HUSSAIN: Let me just share with you the process that we have been engaged in in this instance. We have talked with three universities, CPAC, the University of Washington, with Mel Koch and the University of Purdue and the University of Tennessee and the Measurement and Control Engineering Center, and essentially, we plan to work with these three schools to put a curriculum

together.

And out of some of the discussion, I think the outline of the proposal that we liked most was from Kelsey Cook, from Measurement and Control Engineering and that's what we included in your handout. I think this is a very important sort of item for discussion in this committee. And what I would like to sort of have the committee to just discuss this broadly and sort of give directions. Certainly we will have a working group on that with Ken Morris sort of chairing that group. Maybe give directions to this group and what they should be focused on in developing that curriculum.

DR. LAYLOFF: And so, we're looking for suggestions for Ken Morris and the Education Group, which will be meeting after our break.

DR. SHEK: I went over, I went over what--you know I think attachment, I think PATs 2, looks, I think, very, very good. A lot of thing I observed missing there, there is a section there on pharmaceutical chemical processing fundamentals, but there is nothing about pharmaceutical, you know, drug product and I think it's extremely important to understand the processes that at least today the industry is utilizing, and it's a very

light spectrum. I mean, there's controls release and regular, you know, but I think it's really important to understand the processes and I think this is may a big chunk which is missing there.

DR. HUSSAIN: No, actually, we had internal discussion and we had--we sent this packet out earlier and, actually, we added some of that in.

DR. MARK: Yeah, my comments here aren't directly addressed to the question, sort of they're addressed to the level above it. Because I'm wondering, for example, when the FDA decides to do something like that--to go into a PAT type environment, does it have to go into it all at once and trained all their inspectors at one time or is it possible for them to run some sort of a pilot program where a few inspectors can be trained the performance assess to see where the weaknesses of the training program are and spend some time developing the training program as it's sort of being tried out in a small scale.

DR. HUSSAIN. Let me just clarify that--in the since we have been sort of--the plan that has been discussed earlier, essentially, is we have identified four reviewers, four inspectors, it says

a small subgroup only at this time, so.

MR. ELLSWORTH: Joe wants me to add to that. Yeah, I think in discussing the training, especially for the field investigators, we're limiting it to a certain extent because we need to develop the expertise, but part of this training, I think we're going to be learning as we're doing this, so we want a kind of greater control over the interpretation that occurs, but long-term, we're going to need to train a lot more and we have a whole drug investigator certification program that we're developing and we're looking at a higher level. We have level one, basic investigator, level 2, which is a fairly extensive drug program, and probably a level three will bring in the PAT expertise. We're looking at that now.

DR. SHEK: But my question is, maybe, once we have the curriculum, who are going to be the teachers?

DR. HUSSAIN: What we would--we'd be looking for is the professors from these universities with invited folks from industry who would come and give case studies and so forth. And I think what we envisioned right now is the professors would come, teach in the Rockville area,

so that I think we'll bring our reviewers and inspectors together here and then, hopefully, have hands-on experience at different locations. Maybe some companies would offer some hands-on experience. I know Purdue has offered their lab. So the core group would travel to these places and do the lab themselves.

MS. SEKULIC: I was just having a look at what's listed here, although it covers most of the scientific and technical aspects of what one would require. Two comments, I guess: I don't see a lot on the infomatics side, the software components, the validation. If we are to be developing some of these new technologies, then the partnership with vendors, that's a practical concern that we currently have and that could potentially be a hurdle. I believe that deserves a little bit of attention in the training component.

And I also, like, I think, Ajaz, you mentioned or somebody mentioned earlier this morning the mock sessions, I mean, sort of like play-acting scenarios--I think that's a great way of training individuals and we do a lot more of it in industry for various other reasons, but I think that that's a great training tool of actually

putting people in pre-designed situations. It's a great motivational tool, as well.

DR. MARK: It occurred to me that if an inspector is going to be inspecting new technologies, they should certainly get some training and expertise and possibly by--by actual experience in real cases of using that technology and developing a method, you know, with that technology.

DR. MORRIS: I think the plans are that if they--depending on how it works, but I can only speak for Purdue at the moment, but, I mean, if you come to Purdue to work on the sensor-based lines that we have, nobody is idle. There's--everybody would do hands on is my vision of it. That the didactic part would be here, but that the practical would be at the universities and hands-on, you know, and I'm assuming that that's the case to the extent that it's hands on with--

DR. KOCH: Yeah, I guess if you're getting to some of the discussion we've had within CPAC, we're assuming to take a role that exposing new measurement technologies and sensors that have been successfully in other industries or some evolving technologies and then have case studies involving

that and the data handling that comes from industry participation, as well.

DR. HUSSAIN: The aspect of, I think, pharmaceutical industry participating in the training program, I think that would be feasible. In fact, we felt that the three schools could partner with some companies willing to partner and then have that axis, but through the universities rather than directly, that would be one options.

DR. LAYLOFF: Yeah, I'm sure that the knowledge base is primarily in the industry.

DR. KOCH: I think one thing I might add is I've picked up in discussion with various pharmaceutical companies, a tremendous interest in the later phases of this of them wanting to have their employees participate in some level of this to hear what it is that the reviewers are hearing so that there's a commonality in the language and the success.

DR. LAYLOFF: Yeah, I think, probably one of the greatest incentives in PAT in adoption in the industry is having FDA go out and get trained, because then they'll all want to get trained also, drive everybody.

I guess we can move on to the next

question, Number 4f, on page 5, it has to do with mechanisms for review: What other mechanisms for both NDA and ANDA do you recommend for consideration by the agency that a new drug development process may not be delayed due to the use of new PATs?

DR. CIURCZAK: If I can comment, because one of the things that we've always done with near infrared, for instance, is you have to have a validated method backing it up. And anybody I've ever recommended it to is get your NDA in with your standard HPLC and everything else and then send your NIR method in as an amendment. The same thing could be if everything we're going to do in process is still going to need a backup method, NLC or a Carl Fisher or something else that you're going to calibrate it with. If you're afraid of delaying your NDA, you might, just as well, put your NDA through with the classical assays and then phase in either all at once or several each month or a year whatever down the line to go to PAT.

DR. HUSSAIN: Emil, you just redefined the risk that we are trying to address with the questions--

DR. CIURCZAK: Well, in any case, this

goes back to scaring, you don't want to delay because the financial thing down the line and I don't think anybody's afraid that their products are bad, you know, down the line. But I think you have a lot of financial people up there saying we have a limited lifetime, if this adds six months, nine months, a year to it getting approved, we're going to lose a bloody fortune here and be open that much sooner to competition, so, if you're going to have to develop traditional methods to validate these all anyway, you could always, if you're afraid of putting any of the PAT through, just do your first NDA that way.

And just one more comment, from my experience, the three batches that you have to get an NDA in, they're usually not enough, they rarely give good process information anyway. We like--I like to develop my NIR methods on, like, a year's worth of batches. So, go get your product out there and then start collecting data.

DR. LAYLOFF: I think that the training program for reviewers and inspectors for PAIs will help considerably. Also, I think the open door policy that Ajaz has espoused that, you know, you can come in before hand, you can come in and

discuss it, and actually work out the details on this before the submission. I think that the trained cadre, plus the open door to discuss these issues before the NDA actually hits will get around a lot of that.

DR. HUSSAIN: In a sense, I think one of the proposals that we have is we could actually structure and have special separate meeting with IND and stage at phase II where the concerns would not be an issue. So I think, I don't want to take the negative attitude or get the NDA out and so forth, I mean that's all we are thinking I think we can do better.

DR. LAYLOFF: I think rather than dropping it over the wall to actually come in and discuss it would actually be better than kick it over the wall. Okay.

Going on to Question 4g: What other clarifications should be included in the general guidance on this subject?

DR. LAYLOFF: It goes to Risk 4 which is that this would be a requirement and we're saying it's not a requirement and this is voluntary. And we want to state--that will be stated in the guidance that this is voluntary, and so forth,

should that be--we hope that that will be enough, so.

DR. LAYLOFF: Will that be enough?

DR. BOEHLERT: I hope so.

DR. LAYLOFF: Judy says she hopes so, that's good enough for me. Going on to question 4h--wait a minute, did I just do that? No, that's it, yeah: What other approach do you recommend for consideration to address this concern? And that is, will the company need to use both PAT quality methods and conventional methods for regulatory purposes forever?

[No response.]

DR. HUSSAIN: To give you an example, the case study I constructed with the dissolution, doing dissolution with online assistance and so forth. The criteria could be you have established a correlation and to some degree, you have actually explained that the correlation is just not a black box, it's related to the formulation variables. And if that is acceptable, then that becomes the routine method. And so, dissolution testing for release may not be necessary at that point. And you may need to do dissolution for stability and shelf-life determination only, unless you have a

method that even picks that out, so--

Dr. KIBBE: Let me address that one other little thing that we kind of talked about a little bit before we went to lunch and I think applies in here. And that is, there are times when what the Agency is willing to accept is not everything that a company feels it must do in order to get approval at various places and for various purposes. It's always good for companies to be able to carry a USP imprimatur for marketing sales reasons and what have you and if the PAT allows us to bag dissolution testing but then they can't say that they meet the USP monograph and things like that--and I think there might be an opportunity here--I know you're going to correct me--

DR. LAYLOFF: Okay.

DR. KIBBE: --okay, but I know that companies think about doing extra things to get different kinds of classifications. And whether it's the USP or something else. And one of the things that we need to consider here as we move forward with PAT is how does the Agency get actively involved in making sure that anybody else who's regulating or whose approval is useful to the company is being brought on-board with us, so that

if we move forward with a certain kind of acceptance level for PAT, what is the Agency going to do with it's colleagues around the world to make sure they're moving forward. That's where, I think the only other approach that we need to take in this area is. Okay, now you can correct me.

DR. LAYLOFF: Okay. A USP product has to meet the USP standard if tested. So if you have a process of assessing dissolution and you validated it and you released product without doing the dissolution test and you have stability data showing that it will meet it throughout the lifetime. If tested in the marketplace it's presumed it will meet, if it doesn't meet then it's an illegal product because it doesn't meet the standard. So you have to establish a validated process, you have to have stability testing, but you don't have to do the USP tests.

DR. HUSSAIN: In many cases, I think--or in most cases, you will have a traditional dissolution test established for that product, so you'll have that, but you don't have to do that on a routine basis to release the product.

MR. : But you have to do it to

have USP on the label.

DR. LAYLOFF: No, no you don't. Judy, tell 'em Judy.

DR. BOEHLERT: If you manufacture a product that has the USP monograph then, by default, it is a USP product, you need not label. You need to label the product, if you want to declare it non USP, that's a fact. USP, in the general notices, allows you to test it by other means. That's allowed. And so what Tom says is absolutely right. You know, you need not test, but if the product is picked up in the field, it must meet. So you need--if the USP method doesn't work, you've got a big problem, if your product fails the USP method, you have a big problem and you need to address that, but you need not test by the USP method and you need not label your product USP, it is USP if there's a monograph. You need to label it if it's not USP, and there are products out in the marketplace now that are labeled non-USP.

DR. LAYLOFF: But there has to be a rationale for non-USP--

DR. BOEHLERT: There has to be a rationale--

DR. LAYLOFF: --it just can't be

arbitrary.

DR. BOEHLERT: --and you have to put on the label why it's not USP, I believe.

DR. LAYLOFF: Right, okay.

MS. CHIU: Even today without PAT, not all the products are released based on USP tests, because under our regulation would permit alternate test for routine batch release. Now, alternative test needs to be equivalent or better than the regulatory test which could be the USP test. So, therefore, with PAT, if you have validated your technology and to be equivalent or better, then standard dissolution test, you won't need to do that and based on the validation data, you are sure, you know, every batch will meet the USP test, which is lower standard.

DR. LAYLOFF: Another thing, and I think--and that is if the--having worked in FDA for about 20 years or more--one of the things that you find is that if there is an FDA approved standard and a USP approved standard, if a product fails a USP standard but passes the FDA approved, compliance won't take an action. If it passes--an FDA-approved standards. If the USP standard changes but it still meets the NDA standard, you're

going to go with the NDA standard. So the--in general, if something's going to happen compliance-wise, it's going to fail both.

DR. CHIU: Yeah, that's true, in either NDA or ANDA we have a regulatory standards which may not be the same as the USP standard, but it is always better higher than USP standard. At least it's--if it's equivalent then they will issue a USP test.

MR. CHISHOLM: Okay, I'm in a fortunate position of not knowing what USP is.

[Laughter.]

MR. CHISHOLM: And in the industry I came from, petrochemicals had to do with piping standards, actually. Coming back to NDAs and the problem is all about the size of the data set because, as this gentleman across here said, you've still got to have traditional methods to actually model in the first place. So you've had to do that work, the problem is your data sets aren't large enough and when you scale up, you have to expand your models.

I think you have to--when you make your--and this is just a suggestion--when you make your submission, you have to have the methodologies

in and the work done at the lower-scale level. And that will be done with raw material specs, it'll be done for blending, and then it'll be done if the quality assurance side tablets in terms of active content, whatever you're registering.

You then have to build in that. You won't actually use that for product release until you can validate it. You can't validate it until your data sets are big enough. So I think you're forced down that line whether you like it or not.

DR. CHIU: Well, I think that's a good point because of a compressed depression time, you may not have enough data set, however, this applies to many other things as well. As it says in specification, you know, we had a big workshop and we discussed, you know, during the development time, you may not have enough data to establish the true meaning and the 3 sigma so, therefore, you won't have, you know, the right acceptance criteria. I think that it will also apply to a PAT with limited data, as Jeff mentioned this morning. Maybe there's some kind of change control, or a post-approval commitment, then we can set something interim.

DR. LAYLOFF: I have to tell a little

story. We were doing the Prednisone in vivo in vitro correlation and we found this one product which failed the dissolution standard but which was bio-available. But it was an illegal product because it failed the USP limit. We never took an action because we thought it would be very awkward to go to court and see somebody's product we knew was bio-available, just because it was a technical violation. And the guy who did it said he wasn't going to reformulate because we had demonstrated his product was good.

Going on to Question Number 5: What information should be included in the proposed guidance on product process development and percent analytical validation?

DR. HUSSAIN: The way we phrased that question, that becomes sort of a working group question--

DR. LAYLOFF: Okay.

DR. HUSSAIN: --this is a broader question. And I was hoping is you'll use sometime here to define the charge for the two, three working groups and let them go at it.

DR. LAYLOFF: Okay, so we have defined the charge for instructional program pretty much?

DR. HUSSAIN: You already did.
DR. LAYLOFF: Yes.
DR. HUSSAIN: So, the two working groups processed and--and validation.
DR. LAYLOFF: All right, what do we want them to look at? We have Judy and Art chairing those committees.
DR. HUSSAIN: For starters, I sort of posed questions this morning. On the two pages, you have those. That could be one. And on the back of my handout, I have a list of questions that we received from Merck. So that could be the set of questions. One approach could be here are the set of starting questions and the technical folks will get to the working group, use that and sort of start defining their charge themselves, that could be one approach.
DR. LAYLOFF: What are the questions that you handed out and the questions that are cited in your presentation for guidance. Is there anything else we need to discuss before we break for the sessions?
MS. REEDY: All right, the break-out rooms will be supplied with the break food and drinks. So, the ones in this room are for Room A. And Room

A in this room will be Process and Analytical Validation, chaired by Dr. Kibbe.

The next room, south here, is Room D and that'll be Produce and Process Development, chaired by Judy Boehlert.

And the last room, at the end of the hall, Room E, will be Analytical Technology and Training and chaired by Ken Morris.

DR. LAYLOFF: If there are no other items then we will take a break now for 15 minutes and reconvene in those rooms and not reconvene here today, but reconvene here tomorrow morning.

DR. HUSSAIN: And the working grouzp members in the audience could choose to whatever group they need to go to and they would like to go to, so--

DR. LAYLOFF: But the training group we wanted all the academics to go to the training room.

DR. HUSSAIN: Yeah, correct.

DR. LAYLOFF: All the academic people are banned to the training session and the others may choose their own session, and we will reconvene here tomorrow morning at 8 o'clock. So you have a 15-minute break now; go to your session. And then,

at the end of that session, you're free for today.

And then tomorrow morning, 8 o'clock here.

[Break.]

DR. KIBBE: It's my hope that we would all spontaneously want to get together and carry on this afternoon, that people would immediately want to stop doing whatever they're doing, which I'm sure is extremely valuable to get back to do what we think we need to get done. And so, rather than calling you to order, I'll welcome you back.

This room, we're going to validate process analytical tools. Would you like to validate?

MR. : Yes.

DR. KIBBE: Hi, guys. Look at them all hiding back there. All right. This is a subcommittee and the purposes of it is, of course, to review some of the information we've done in the past, some of the thinking that we've had in our various meetings and come up with some recommendations for acceptable guidelines for validation of the PAT processes that might be put into place.

And I see around the room experts in validation, I can tell by looking at them that they probably know so much more than I that they're just

going to leap forward and give us the correct answers. I have a very simplistic way of establishing a valid analytical method. You do it, you show it to me, if I like it, it's valid. That's the old FDA method of approving anything. But we're going to try to be a little bit more scientific and actually come up with criteria.

So they didn't give me any speeches to make and I'm a university professor, I can talk for 50 minutes on no topic at all, but I can't talk for 3 minutes on anything worthwhile, so let's go with validation.

How would we recommend that the Agency set up it's guidelines for accepting a PAT in place of or in lieu of or as a method of superseding a current method for approving a process or a drug product? We have seemed to have focused on oral solid dosage forms, although my good friend David, who has disappeared, talked about suspensions before and I think we have to remember that we are talking about any kind of dosage form, but it seems pretty apparent that oral solid dosage forms get the most interest. Maybe because there's more of them and maybe because there are some opportunities there unmet before. Anybody would like to comment

on how we validate? Somebody's going to comment, thank goodness.

DR. MILLER: I'll just start a discussion--just kind of start with a question here, is it a reasonable thing to take as a starting point, what's currently done for validating laboratory analytical methods and see what needs to be done to those in order to make them applicable to a process system?

DR. CIURCZAK: Two people--when we were at the--I think it was last month--at the Advisory Committee meeting and they made the concept about sensors versus analysis. Rather than thinking within--and I hate this term because every commercial in the world uses it--with that, instead of thinking inside a box, we're so used to being analytical chemists, where we have to come up with a number, 98.75730201 and round that down one, instead of just saying good, bad, or indifferent.

If we're going to set up a set of sensors throughout a process, we may not need to know an exact answer, that any one of those--this is for the USP concept--I hate going back to that. But if you look at something like lactose, you boil it up with copper oxide and if it turns red, you've got a

reducing sugar, you put it in ammonia and you look at the optical rotation. No one of these things is definitive, they're all circumstantial. But it all adds up to a quality or an ID for a product.

The same thing when I used to be talking about near infra red as a final release and everybody was saying, well, it's a single test, you have trouble with things like specificity. And I'm saying, no, it isn't. The trail of evidence under FDA guidance is stricter than anything the FBI ever had. From the minute that we quarantine raw materials and start doing tests and there's labels and they're quarantined and they're shipped with paperwork and signatures, and even to the point of two people signing off the weighing of them into the blenders and it's validated this and validated that, by the time you get to, say--and I use NIR because I make a living at it--using NIR for final release it's the last in maybe 25 or 30 tests. You know what's in there. You have a pretty darn good idea from the batch record how much it was, that everything along the way was there. So, I think what I'm trying to say is that any of these tests and to answer Howard in a long way--need not necessarily look at all 29 for 500 of the ICH

guidelines specificity linearity, et cetera, et cetera--we might have to be able to just bring it down to a certain amount.

If we're looking at pH for a flowing system, you know, all we have to do is show that it's linear between 4 and 7 or whatever, because you can get carried away with all the rules and guidelines. As I said, God only gave us 10 SOPs and look at the size of the regulatory committee that we have now between the mullahs, and the priests and the rabbis.

The, you know, we don't want to overdo it, the KISS, I think should apply here, to keep it simple stupid. We use a lot of inferences, I think, would be a good way along here.

Weighing the tablet--if you've shown everything is perfect and the blend is perfect and you've got a validated tableting process, you should be able to weigh it. You know, something as simple as that. We would tend to think of fancy spectra and chemometrics, but how about weight, or hardness, or color or something like this.

That's all I wanted to put in and we don't need to, necessarily, in my opinion, go to extremes for every single one of these tests that we put on

line. Just as long as it does what we say it does.

MR. COOLEY: Art, kind of building on, I think what Howard was saying, was, you know, it's good to start at some point and the ICH guidelines may be a place to start. But I think the issue similar to what Emil's driving at, too, that there are some applications where that makes sense and there's going to be some applications where that doesn't.

Looking through the minutes of the previous validation meeting, it appeared that there was an attempt to kind of pigeonhole PAT in one box and it was even referred to as inferential measurements, I think. I'd like to throw out an idea to, maybe, think about this in a little bit different light. And that is I don't think of PAT as necessarily an inferential measurement. It can be just as specific as any laboratory test, but it could be just as inferential as a pressure transmitter.

So if you could kind of look at on the extreme left, having inferential measurements, like, pressure, temperature, flow, volume--things like that that we typically use to control our processes. And on the extreme right, laboratory

methods where we do need all of the specificity and so on because they release assays. And think of PAT as kind of a bridge between those two, where to the extreme right you have PAT methods that may be every bit as accurate and specific and precise as a laboratory method and in that case, you could certainly use them in place of laboratory release methods and they would need to be validated to that level.

But on the far left, you may have things that were an online analytical measurement may appear to be more in the realm of a pH or--I'm sorry, of a pressure transmitter and you would certainly validate it in that way, if that's the way it's being used.

DR. KIBBE: I think you made a couple of good points and I want to make one other one. We keep talking PAT, but that, in my mind, is a group of technologies and they're not all the same. And our colleague over there is doing near infrared and, you know. I know how to do a blend, when I'm adding one pink ingredient. I wait until the color's uniform when I see it and I don't need any fancy equipment. I can look at it and it's all a uniform color. That's how I do my paint when I

paint my walls and ceilings, right? Oh, yeah, we paint them.

But in any event, I think you're right. I think what we are faced with is--depending on the technology that we ware using as an in-process tool to clear our batches or monitor our process, we have to have a different validation. And it could very well be that blend uniformity, as determined by near infrared or some other probe in our blend, can only truly be validated if we get to what we think is an end point at blend uniformity and that blend results in a truly uniform batch of tablets.

And would that be good enough for the Agency? It might be good enough for me, but would it be good enough for you and if that's the case, we can have real simple validations for some things and others more complex.

MR. COOLEY: To comment on that. You mentioned validation that's tied to a certain technology. I would propose that the validation be tied to its intended use and not the actual technology.

DR. MARK: Yeah, that's essentially what I was going to say. It seems to be at least as much the application because it might me--in some cases,

I was thinking you might want to make a simple test with controlling the process. Say a company learned that if they controlled the--you know, some parameter, I'm not even going to try to pick out a specific ones, some controlling some parameter controls the process adequately for their needs. But that wouldn't be enough to satisfy the regulatory requirements. When they got to the end, they'd still have to do a separate set of regulatory validation measurements for regulatory purposes, but the simple PAT test would be enough to keep the process in control.

On the other hand, they might have a whole suite of tests in the PAT and that would simultaneously satisfy the regulatory requirements. So, you know, there's a whole range of possibilities of how it could be applied as well as to possible technology and that that would determine how much validation was needed.

DR. KIBBE: Let me turf a little bit of what you said to some of the people at the Agency. Isn't our intent here to develop ways of replacing the standard testing with process-testing tools and if, in fact, that tool is predictive of the outcome, isn't that the direction we want to end up

going?

MR. FAMULARE: Yes.

DR. KIBBE: I love, true/false, questions. You have to push the button so we can hear you.

DR. WOLD: So, I think that we have to sort out two things. One is what PAT is used for and the other one is process control. Because if we start to mix in process control and if that has to be validated, too, I think that FDA's role will expand greatly. That was not your meaning. So it is very dangerous to have this control within the purpose of PAT. PAT's purpose as I understood it is precisely what you said to be used instead of other traditional chemical testing.

Traditional chemical testing is not used for process control. PAT can, if you want, be used as process control, too, but that is not--

MR. FAMULARE: That's already an expectation for process control even under the current paradigm because you wouldn't be able to achieve validation without control.

DR. WOLD: Yeah, but--

MR. FAMULARE: The difference between today's paradigm and the hoped-for paradigm with PAT is that you'll have more data. We'd hope with

more data you'd be able to better control the processes for a more positive outcome as opposed to, I think, they way of thinking as you expressed it, that FDA is looking exercise more control.

We're looking for you to exercise more control--

DR. WOLD: Yes, for sure.

MR. FAMULARE: --so that we could step back from these actually indirect ways of looking at things from just limited data sets.

DR. WOLD: But that's the way you use the data from process control--under process control, does it keep the process at the right temperature, right speed, whatever, that is to say, together with all other processes that they are in a certain range.

So, for sure, if you want you can use control data for also PAT, to ensure that your product is okay. But I think that it's very unfortunate and very confusing if we start to mix. Because, let me make a direct question to you. If you--if somebody comes in and say I can't have a better thermocouple to control the temperature in the inlet eye of a drier, does FDA have anything to do with that? Or if you say, no this measures the

temperature and this is fine. I don't think FDA meddles with how people control the process from a technical engineering point of view, do you?

MR. FAMULARE: That is, that can be a GMP issue as to--in terms of a root cause as to why, you know a processes does or does not work.

DR. WOLD: Yeah, sure.

MR. FAMULARE: Whether it be a thermocouple in a heat for a drier in sterile processing, it's critical in terms of monitoring autoclave temperatures, et cetera--

DR. WOLD: Yes, but--

MR. FAMULARE: --so I don't know, I'm not quite clear how you are segregating the, you know, qualified equipment is important so--

DR. WOLD: --my question is, do you--

MR. FAMULARE: --it has nothing to do with PAT, it's just--

DR. WOLD: --yeah, but the problem is, I see, we are discussing two things. We are discussing PAT to substitute testing, as you said, and that's one straightforward application and we can eliminate a lot of traditional testing and put PAT there, instead, because it measures basically the same things, but in a better way and perhaps,

indirectly we are lots of signals, but it's basically the same chemistry we're looking at.

But then comes the second thing is, of course, once we start to do that we can then use that also to detect upsets or out of specifications or what do you call it. And then, we my have to do something. And that is the process control.

And then, if you have an operator doing things, you call that open loop. If you take the PAT equipment and actually wire it so that it will, itself, correct the process, then you have to do a lot of identification and process control modeling and so forth before you can do that, but you can do that, too. But I think that's far beyond what we are discussing, because it becomes much, much more complicated and it was not the original intention. I can see that this discussion gets out of hand, so let me back off and say that, if we now go back to what I consider a traditional or accepted objective. For PAT to be that in a certain way, you have to have the same requirements in that as any other testing.

The problem with PAT is that because you have much more signals, usually, it's more difficult to keep track of all things that happen,

so you have to have more--a more elaborate strategy to find--to change the conditions of the process. Much too, too high concentration of active ingredients and too low and too much excipients and too little excipients and too much blending and too little blending. All of these things together, and I think one should follow design, otherwise, you can never do validation. So, that was what I was trying to say.

MR. FAMULARE: Well, I think, maybe, that's--part of what you're saying towards the end there is probably an issue for the training group in terms of you're going to be looking at a different data set as FDA, you're going to be looking at a different data set as manufacturers and we have to learn how to deal with that rationally, reasonably, and scientifically. And I would agree with that.

But in terms of, you know, the stated purpose as Arthur has expressed it, yes, you know, it can eliminate the need for conventional testing. You have out of specs, as situations now with the current paradigm. Our hope from a positive aspect is that this will either, number one, prevent all those out of spec or recall or other manufacturing

situations that limited data can address; and, secondly, to, you know, to be able to, maybe--if it is legitimately out of spec, be able to pinpoint the problem better as opposed to having it, you know, an indeterminate, with no other alternative than to dispose of the whole batch. So we're trying to look at it from those positive aspects.

DR. KIBBE: Let me get us back a little bit on--I assume you're going to go back to validation--

DR. MORRIS [?]: I think we're mixing--we're getting confused because we're trying to look at too many things all at once. We've really got four things we need to look at here. I think we need to look at whether this technology is controlling the process, number one, or whether it's monitoring the process, number two. And those are--while they've got many similarities, they have some very important differences.

Number three is it a direct measurement, or is it, number 4, is it an indirect measurement? An example of a direct measurement would be, let's say an ERI analysis of an active ingredient and a tablet. An indirect measurement might be something like a hardness or something related to

dissolution; it might be a temperature measurement, it might be a blender rotation speed, it might be--it might be all kinds of things.

So I think we have to keep these things, at least for a while, until we can clarify our thinking in separate boxes.

MR. FAMULARE: Right, and when we talked, about, I'm sorry--

MR. LEIPER: Thank you. I've listened for a while now and, with all due respect, I think that we're probably looking down the telescope from the wrong end because if the answer lay in what we did today, we would sure as hell know how to do it and we don't.

And the thing that's lacking and it's been going around this room all today and it went round the room in the Holiday Inn for two days four months ago, is that we've got to understand the need. And the need is driven by our processes. We've got to understand our processes so we can't accurately talk about validation of process analytical technology until we get into our minds that these processes we don't know, actually, how they work.

And one of the problems that we've got and

had over the past is that we actually use univariate measurements inferentially to describe multivariate dynamic systems. Now, if we're going to get anywhere with this, we've got to understand that multivariate nature.

Point number one, about validation: when you validate a technology that's capable of a multivariate assessment and you use an inferential univariate measurement, you just might have an awful lot of trouble on your plate. And the blend uniformity working group is a very good example of that. You know, we--it's taken us two years to find out that we're really no further forward than we were two years ago because we were looking for a quick fix rather than something that actually took us far, far closer to where we want to be.

So the first thing is that we've got to understand the processes. Now that's not just unique to manufacturing processes. We've got to understand our analytical processes. Now, if you think about our understanding of analytical processes and go back to the blend uniformity working group, there's one thing for sure: With equipment qualification, we know that the qualification equipment's okay, we know with C.F.R.

2111 that the data management's okay. But if we do a risk analysis of an analytical measurement and take it from the sample preparation, the measurement, the data acquisition and reduction and the production of the result and we look down the right-hand column and say where's our maximum risk? The maximum risk is sampling the process, so it doesn't matter how much effort we put into equipment qualification and C.F.R. 2111, if we don't get the first bit right, we've actually got big, big trouble.

So, you know, we can't just launch into this about pH measurements and all that kind of thing. We've actually got to understand these processes and take a step forward and say what types of measurements are going to allow us to facilitate that.

Now, wouldn't it be good if these measurements, these multidimensional measurements not only facilitated process understanding and development but, also, facilitated control and manufacture?

Because, if you look in your--if you look in your backgrounder and you go to Ray Sasher's [ph] presentation and this was done on behalf of

CAMP, you will find that the industry has got low utilization of manufacturing processes, 30 to 40 percent on average. And that's probably on a good day. And we get, on the next page that a 1 percent yield improvement--now bearing in mind, we've only got 30 to 40 percent efficiency in the utilization--a 1 percent yield improvement would yield probably very conservatively $400 million in savings across 16 companies per annum. You know this is what--this is what we're gunning for and the beneficiary is the public. So, it's got to be process understanding. It's got to be the right methodology, I believe and the same principles for looking at validation or the structure of validation in processes, it doesn't matter whether it's the manufacturing process or it's an analytical process, it's exactly the same. It's understanding the risks, it's managing these risks and having done all that the validation is actually proving that you've managed the risks in the way that you have described them in that process.

So, I think we've got to get something far more fundamental than we've been looking at in the past or, indeed, today.

DR. KIBBE: Okay. So, you're going to

have to help me, okay? So, I'm all excited, I can't wait.

MR. LEIPER: You're all excited, Art.

DR. KIBBE: I can't wait--I cannot wait.

MR. LEIPER: Watch your pacemaker.

Dr. KIBBE: Right, my little pacemaker's going, you know, pitty-pat here. We, I think, intuitively all understand that whenever we make something, there's a processes and if we want to make exactly the same thing each time, we follow exactly the same steps and we should come up with the same result. And if we don't, then we might not end up with the result. And so, if we can find a way of keeping track of all of our steps, at least the critical ones, then the outcome will be fine and I don't have to do terminal testing, right?

So, now we're looking at process analytical tools or assessment tools to be able help us do that and what we want to know is what kind of a guideline can the Agency develop that will help industry feel comfortable that what they do to validate any tool is going to help them know that the tool is working well?

MR. LEIPER [?]: I think it's quite

straight forward. It's the same as in any other industry. You actually--you understand your processes, you identify the critical areas, you categorize the risks and you manage these risks. And some of them you manage in terms of, with a PAT. I mean, some of them, this morning, when we were talking about an SOP to get ingredients in a blender and in the right order. A bar code reader's only $300 or something like that and we can actually make sure it goes in in the right order. We don't have to have bits of paper that we would sign to say that these kind of things happen. There are very interesting technologies that are used in your supermarket that will actually do that for you. You know, and we've just got to think differently, we've got to think out of the box.

MR. HALE: I think that--I agree with all of that and it gets back to a design issue of thinking about not using sensors, but thinking about designing what you're doing and a lot of it falls out.

Another think that hasn't been talked a lot that is an issue in these are specifications. Because we define specifications very early and we can, therefore, tie our hands based on the way

specifications are written, the methodologies that go into specifications, so that the freedom to optimize or to measure to improve or however that's defined, is controlled before a lot of other things happen, like scale-up and manufacturing and so on. So I think that we--one effort that could help us define how to do the specifics of validation could be looked at as a function of how we write our specifications or how we do--or in another way, how we do the release of either the product or unit operation.

And I think it could be defined somewhat along the lines that was earlier talked about into three different categories.

One would be the traditional way that we do this, where we take samples after a process is done and the process is defined within strict or strict or not strict, but within parameters that are static. And that the testing of either the unit operation or the product is done in a physical chemical sense in a laboratory away from the process.

The other one would be a process that is controlled and the product quality is inferred from the data on the process.

And the third way is that if the product itself is actually measured, and that the process is controlled to allow product quality. And if you look at blending, you can take--in those examples, as a unit operation, you can take these samples based on rotating a blender a fixed amount of time, based on development data, one would presume, and take a sample and test it off line. You could measure the processes a number of times, or you could actually have a probe that measures the uniformity somehow in there and that the validation would be defined differently for each one of those cases.

DR. KIBBE: It's my impression that often when the industry looks to the Agency for a guideline, they want us to tell them that you take these number of samples now and you do this and you do that and you that and that's validation. And I think, what we need to tell them is the general rules and let them establish it and I wonder how many of the people who are industry people out there are comfortable with that? Know that the way they interpret the rules is then going to be further interpreted by Agency people?

MR. LEIPER: You know, I think it's quite

clear that, you know, that there have been claims over all these meetings that we ought to be able to scientifically justify what we do. And I think that it's incumbent on the Agency that it's actually got scientifically review the information that's provided. And, you know, I think that these are pretty big burdens that we're going to place on all sorts of people, but traditionally, what the industry has been looking for is an--when they ask for guidance, they want an instruction. And the instruction is that if we do this and the FDA come in a look at, then it'll be okay. And it doesn't matter what the hell happens to processes because we can live with that in 40 percent efficiencies. I mean, that's the indication.

You know, so, we've--it's breaking--it's actually breaking that mold. And I think that a lot of that was done when we went to the equipment qualification. It's fascinating, we wrote GMP, we then got into that in the '70s, the '60s and '70s. We wrote a validation--guidance and validation in the '80s. And in the '90s, the early '90s, '91, I think it was, we wrote equipment qualification. And then in '93, we came up with something and wrote the specification results. Now, you know,

logistically, it's all in the wrong order.

Equipment qualification, however bad it was had to happen first. You know, because you can't do anything unless you know that the equipment is actually working in some sort of way. And then you can write--you can begin to write approaches to GMP and then you might be able to write something about validation. But, over all that period of time you were dealing without the specification results, not too well, I may add, but we were dealing with it.

And this is an opportunity to put these things into perspective. And I think that the model that you've got for equipment qualification is actually a good model to follow because it starts with design qualification. If you don't know what you're trying to do then you'll never make it.

You then go to installation; you go to operational and performance qualification and performance qualification, to all intents and purposes, is interactive validation. Revalidation. If you've got that right, that's what happens.

The thing about that whole system is that it's always referred to as the 4-Qs approach to

validation, but it's not. It's really the 5-Qs approach to validation. And the fifth Q stands for rescue and that's what happens when the DQ has been done badly. And it's all--all this is front-end loaded.

DR. MARK: Okay, I'm not going to say Ken is wrong because he's right--but--

MR. LEIPER: Was that a validation statement?

DR. MARK: What?

MR. LEIPER: Was that a validation statement?

DR. MARK: I think so, I'm validating what he said, but the problem is--as I see it is that what Ken's talking about is a very long-term thing, I mean, years and years of research to, you know, to do enough work on a process to understand it thoroughly--

MR. LEIPER: And the confusion that we've hot, Howard, is that we've got years and years of mumbo jumbo. And if we could get the mumbo jumbo out of the way, it wouldn't take years and years and years of research.

DR. MARK: Now, that may be, I don't know. For better or worse, I've never worked in the

pharmaceutical industry directly, so I couldn't speak to it. But it sounds like you're talking about doing the whole process development, which is certainly something that's necessary, but I think not what this group is supposed to deal with. I mean, we're talking about process analysis which to my mind, you know, does mean a number, even though, of course, I understand there are important things like blend of--blend uniformity, which aren't, you know, a concentration per se you want to measure.

DR. KIBBE: If you don't know what the process is, how are you going to measure it? And how are you going to track it? And if we're going to do process assessment tools, I like my word better than analytical, then--then we have to know what process we're assessing. We do that in education all the time. We think we're educating our students and we assess how well they've been educated and we find out we can't do anything with them.

But what I'd like to do is get some other people to comment. Jerry, you have something, you want to jump in here?

DR. WORKMAN: Yeah, I've been a little bit confused about the overall issue of validation

because when I look at what you're looking at, you're looking at sensor and software validation, you're looking at sensor, the calibration and validation, which involves with multivariate problems a lot different problem than univariate. Then the process monitoring validation, if you're going to monitor, what are the protocols and how is that validated? If you're going to model the process, using that information, how are you going to proceed with that to get a good model. And then, also, the controls. If you're doing process control, what are those protocols and how are those validated.

Is the method a primary method or a secondary method? If it's a secondary method, you need a primary method, so you have to validate that before you do the secondary method.

Is it, are you looking at a direct analyte [ph], an active, for example, or an indirect analyte, like dissolution or are you looking at a virtual analyte, like, how much the customers love this when they take it. Those things are possible, as well.

So in all of this arenas or eras, if you will, there has to be specific validation issues

that are addressed. And they're somewhat, you know, they're somewhat separate in how you would address those. I know, for example, if you're looking at multivariate calibration, it took a group of--in ASTM--it took a group of, well, anywhere from 40 to 100 people 8 years to put together a protocol on how to--in a continuous process do multivariate calibration for infrared and near infrared and how to do the outlayer detection, how to do the monitoring, how to tie that in to closed-loop control and get that many people who were doing that type of work to agree on it, how to do it.

So, there's a lot of specific issues, I'm not sure which one is being addressed. If anyone can help me.

MR. LEIPER: I understand exactly where you're coming from. The point about it is that if you start off at a low level, you'll forget what you were actually trying to achieve. The most important thing is to keep in mind what you're trying to achieve and you can mark down that and you can refine it as you go along, Jerry, I think that's important.

And I think the other thing that's

important is that the methodology--the assessment methodology is inextricably linked to that process that you're looking at, you know. And that's somewhere that we've never actually been before. Because analysis has always been carried out in isolation to the process and processes have been designed in isolation of the analysis. And I think this is where, you know, where the points that Tom's been making all day and at the last meeting, it's important that we actually design--that we actually think about these processes.

It's also important that we--that when we begin to look at this, is that we make--we actually design processes that are measurable. We don't set ourselves Mission Impossible because someone designs a process and no one's got a cat's chance in hell of coming up with a measurement system for it.

You know there's an awful lot of things have got to go into this, but I think--and I think that we come down to the issues that you describe. I mean, for instance, blend uniformity. We know we can do blend uniformity by and end-point-type methodology, that would be a methodology that we would use. The problem that we've got is that the

whole sampling regime for blends is discredited because we know we can't sample them. You know, so how we will use that. Is that the reference methodology for the validation?

It actually looks at the distribution of the active and it assumes--it assumes that the excipients are, indeed, the most important things. Art was talking about this morning and the max stearate is distributed because the active's distributed, rubbish. We know that that is not so. So we've got to put our existing methodology, our existing approach to these correlations--we've got to put it under as many challenges that are justifiable as the new methodology that we're putting in because the problem that you've got with a new method and cross-validating it as an old method is that you could actually be detuning the method--the new method to actually meet the conformance of the method that you know is not doing you any good.

DR. KIBBE: What we've agreed, I think, is that we can't always use existing methodology to validate what we want to put in place; that we have to have validation protocols written for a method and a process by the company that's using the

method and process. And then we have to have some criteria that the Agency can use to say they've written a good validation in their situation.

And then, Jerry's list, which I thought was quite complete is the guideline list for the Agency to say, okay, these are the questions that need to be addressed in any validation. How many of them can be ignored in this process because they don't apply? And how many of them should have been looked at because they do apply? And did the company look at them? Am I getting close to where we are? What do you think, Tom.

MR. HALE: I think that's right. I was just sitting thinking that we have--we have a regulatory and I'm not sure this makes sense at all, but I'll say it anyway. We have a model that we use for filings in the developmental pharmaceutics section of how we got to an endpoint in terms of the product. And I know, I've done this before, but what is--the history of development of these processes might be a way of getting to a validation that there is--that could be a disjointed redevelopment process at each scale or there could be this inherently scalable processes and product. And that might be an

important aspect of what's required to proceed further in validation.

MR. CHIBWE: Yeah, I think that's probably the best way to proceed. Because if you go back, we seem to be going into Phase III, when I believe that PAT is in Phase II. So, when we're jumping to process validation, we're actually trying to go into Phase III for continuous production. If we have the safe harbor, and if it's going to be as protected as we say it's going to be, then the development work itself, should provide the validation that is needed.

In other words, it's going to have the traditional limits, specificity, ruggedness, linearity because that needs to be specified. Because you simply can't measure something and come up with some statistical analysis and just claim this is what I have. You will have, definitely, some reference to a traditional method during your development. And that's when the validation's going to take place.

And if you're going to take everything back into Phase II, I think that's where we should, our discussion should focus for now. And later on when we have developed it to a point where we're

going to go into continuous production, I think that's when we'll probably encompass the entire processes validation.

Because, otherwise, at this point, I think most companies, at this point, would try to use set-in sensors for set-in parts of their process.

MR. CHISHOLM: I finally managed to steal my mike from Ken for a minute, you know. I think we have to get a little bit careful. We're getting a bit esoteric at times here, I think. And I think if it goes too esoteric, it can become meaningless.

We have two different scenarios to deal with. We have products which will probably be in late development. We have products which are out there already. And we have products which we're developing. And I think what you were talking about as going right back as far as Phase II is we have every opportunity in the world to design quality into the actual product and, therefore, it's manufacturing process. So that has a different set of validation criteria, I think, from those currently in late-stage of development where I would suggest maybe a lot of companies will be wanting to submit these and products that we already have that are fairly young and would be

worthwhile submitting. It's very unlikely we'll submit old products anyway.

So I think there have got to be different validation criteria for that. Now the only way that I can see us actually dealing with products in late-stage developments and products already in manufacture is by demonstrating equivalents to existing registered methods. I cannot see any other way because you have not the chance to get the design process right, everybody keeps talking about. So I think there's two classes of problem here when it comes to validation and I think we need to deal with them both separately.

DR. WORKMAN: Yeah, there's been a lot of discussions on--over many different organizations and groups about how to describe the whole calibration/validation process--whether you want to specify exact details in a cookbook fashion or whether you want to treat the method as a black box, where you have--where you thoroughly describe the design of an experiment that goes into the black box, and then thoroughly describe how you validate whether or not what you did in that black box is working.

And, of course, you would document

everything that was done there. But most of these complex multivariate methods, in my opinion, can be addressed by the input and output issue so that you don't have to completely describe every mathematical process that goes on.

Once the method results are obtained and that information is provided, then what you do with that information is the same thing that you would do with standard analytical information if you had it in a real-time basis. That's one way to address it--one model.

DR. TIMMERMANS: I just wanted to make a couple of points. I think, in most cases, we will have an opportunity, if we have--if we implement a process analytical technology-based measurement to go back and compare it to an existing analytical methodology. In some cases, though, I foresee that we may not. And we may actually make an inferential call based on a result that we obtain on a product further down the line. So I think that that's something that one should, you know, should keep in mind.

Also, while I agree with Ken, you know, that ultimately a fundamental understanding of our processes is key, I agree with Howard's assessment

that that's, you know, something that will probably take a while to get to because, in some cases, we actually, you know, we just lack the fundamental understanding of, for example, solids flow, to be able to really understand the blending process. So I think that that should be noted.

My approach--my personal approach and I think a lot of people here, I hear the same thing, has been, you know, to use scientific rationale when you validate your methods. And, you know, to go back to one of Rick's points that he made very early on in this whole discussion is, you know, applicability of the methodology, you know, it can range from something very simple to something, you know, very complex. I addition, you know, we're--essentially we're measuring--we're trying to address a multidimensional space if you will, with this validation discussion and I think there are many components, most of which Jerry brought up. Each of which have their own issues and that may need to be addressed, but I think the, you know, the scientific rationale should be at the fundamental--at the basis of the whole discussion, so--

DR. ANDERSON: Just to amplify your

comments. Right now, and I know you have had experience with this, as well. If we do good science, we can bring that and we could submit the method and we can be doing PAT tomorrow. In fact, that's literally my plan, but it's my understanding of all of us sitting here that we want to make it easier for companies that aren't willing to step out to the front and say, I'm going to do this because I've done the science and I'm going to hope that there's reason in the FDA and things go well.

What we need to have is a tool for us--for me, as an industry person and for you all as people who are evaluating my science, a way for us to connect and for you to easily judge, or at least a framework to judge my science with your investigators. What do we list and what do we put in that framework--what does that framework look like?

DR. KIBBE: And I think that's what I was trying to get at a little while ago when I said we had to take some of your list of things and then let the scientist whose ready to move say a bunch of these items don't apply to this particular process. These items apply to this process, I've done these things and I ruled out the fact that my

result is a function of some variable that isn't under control, that isn't part of the process, it doesn't control--I've ruled those out because I've looked at those and now my process is under control and this is telling me this and this is what I'm going to follow. And I think we have colleagues with would rather have us say, measure these six things, measure two things. And I don't think we're going to get there and I don't know if anybody thinks we're going to get there.

We have opportunities for guidelines that apply to everything and we have opportunities for multiple guidelines to apply to different kinds of things. And should the Agency be in the business of, one, overreaching guideline for validation of PAT or should it be writing 20 or 30 guidelines--one for how to handle active ingredient arrival, one for how to have blend and so on--and I think that's another way of looking at it. I don't think the Agency want's to write 27 guidelines, but they also don't want to be in the business of arguing a guideline with a person who thought he lived up to it when they didn't, either. I mean, that's one of the problems and you have a good one, go.

MR. LEIPER: Well, I--you know, I think that there's been some interesting stuff has happened and what you're referring to anyway, Art, and that is that I don't think the industry wants a compendial approach to this at all because all our processes are actually different processes and they're processes in their own right. They've got commonalities, but they are different processes. And it is interesting to see the approach that the FDA took at the USP meeting on functionality in December, where they said they recognize that the functionality of materials in solid-dosage forms is fundamentally important, but it is process-specific, it's not something that's a compendial--a compendial issue. Which puts the onus back on the people who are responsible for the processes, i.e., the industry, to actually, scientifically investigate and defend the stance that they've taken--that they're taking. But I--and I think that the good thing about these meetings that we're having is that it's bringing the industry and the regulators together because the industry's got the processes and the regulators don't. And it's that--it's establishing these linkages in a non-threatening environment, may I

say, that's actually important and will take us forward.

DR. WOLD: Now, I think that those who say that PAT can be validated in the same way as any other equipment or whatever, in principle, are correct. But if we go back now, see what is specific with validating analytical technology. I mean the first thing is that any analytical technology is put interest the process or after the process to measure certain or to deal with a certain problem. If you want--if you say I want to make sure that I don't have too much or too little of active ingredient, then you develop an analytical procedure for that and then you validate that by first of all saying that, if I have too much or if I have too little, it really shows that I have.

Then you have the second problem that each analytical method is reacting to other things, to disturbances and the interactions and so forth. Now, you have to make sure that the normal disturbances you have--in my process I have excipient that vary a little and I have temperature and I have humidity that these don't disturb my measurements too much. So you have to vary these

and show that your measurement behaves okay.

Now, the real problem comes after that, I think. And that is in the real process there will be a number of new disturbances, that we haven't thought about, indeed, we haven't understood. And process analytical technology, based on spectroscopy any other multidimensional sensors, they are more sensitive to the whole world of new disturbances, which is a very good thing because we see them. But that is also problematic because we don't know how to deal with this new information and I think this is what we are, so saying, having great difficulties with.

The first two, to have evaluated as any other univariate or few-variate method we can deal with in a very straightforward way. But to say that optimistically, now processes analytical technology will solve all future problems. Then we have in the validation in some way to incorporate, also, all future problems and that is a very great difficulty. And we have to go piece-wise. And I don't know if FDA is willing to go piece-wise and say, now we have this operating as well as traditional methodology and in five years we shall see from real production how well it actually

caught unknown disturbances that we haven't seen.

DR. KIBBE: Let me just see if I've gotten some of what you said and put it in my own parlance. If we put in a new took, which is naturally more sensitive than the old tool, then it will find variation that wasn't there before, just because its sensitivity is up. We pertubate the system to make sure it actually can notice changes that we make in it so that we know it actually is going to measure changes and not ignore them. and then we decide at what point we're happy with the variation it sees as being within limits. In other words, we set our limits of its variation to match up with what we've already got. All right?

Then we stop doing the second thing or the original test and we now depend on this new system, but we don't know, five years from now, whether it will miss a change that the old system wouldn't have missed. Is that part of our concern?

DR. WOLD: No, it will see all the things that the old system saw but we know that the old system we have today, is not adequate. Any system we put in is inadequate for everything that happens in the future. So, we want to simulate in some way the real variation in the production, including

what we don't understand and this goes back, now, to Ken, who says we don't understand our process. We will never understand our process fully. That's impossible, because it's more complex than our brain.

MR. FAMULARE: It almost sounds, though, you know, under the current paradigm you do the process development work, you have your standard analytical tests, you feel comfortable with the process, you represent this as your specifications and you validate against them and the process goes along for five years and you find something, you deal with it. And, you know, you may have to investigate what caused that change. Now, the way you're describing it, you'll--and I may be getting it wrong--you'll put in a PAT process, it's more sensitive but, hopefully, we've factored in the sensitivity against the specifications so that they're statistically and scientifically rational. But then it sounds like you still want a five-year, 50,000-mile guarantee on it and I guess it would be a similar parallel to, you know, any unknown that might come up in the existing paradigms--in excipient changes or something happens. I don't know how we could satisfy that concern that you're

raising in that format and how PAT is making you any worse for the wear.

DR. WOLD: If I may clarify a little. I mean if we take, say, near infrared spectroscopy, we know that we cannot see the differences between different vendors of excipients. Now we are not quite sure if it really matters, if this difference matters. But we suspect that it may matter sometimes and we--with multivariate sensor techniques we can see much more. That means that today we know from a scientific point of view that actually the old way of writing specifications we're just saying we need content uniformity and we need this and we need that that is inadequate. And we start to see that already and we start to have a lot of process problems, the list of your directors was very revealing in that way.

So the process analytical technology brings hope we can see more, we can be more realistic. But the question is, we can validate and say we do the same lousy job as our present measurements do, but that is not really what we want. We want to do better. And the question is, how do we validate that when we are not quite sure what better is? But maybe I'm too academic, I

don't know.

DR. WORKMAN: Well, at the risk of over--I'd like to get back to that but I was--but at the risk of over-simplifying, I think the validation procedure should include a rationalization for what information's needed, where it needs to be measured, when it needs to be measured, how the information is used because if you put enough sensors on the information or on your process, it's sort of like, I think, raising teenage kids, you don't want to know everything they're doing, otherwise you'd be changing their lives an awful lot more than you should probably. If you know everything about the process how do you deal with all this information? And then who interprets it and do you throw out the bad stuff and keep the good things to make it look good or, I mean, there needs to be protocols, I think in all those areas, but a good scientific rationalization for each processes.

DR. CIURCZAK: One of the things I was thinking of is we seem to be either or. One of the reasons you might want to slap a dozen or two sensors on a system is, literally, for information purposes. And if you watch it over a course of a

year and you notice that when the moisture goes up, you have a higher reject or you have tablets don't dissolve, you now know you can control the moisture. Now you can take that measurement tool and use it for a control tool.

The same thing with anything else. If the hardness doesn't seem to matter--if you go from 2 to 20 and your release rate's the same and everything else, you can can hardness. I think that, again, we can't a priori know what is an important factor because as, Ken, who is one of the few people that I found in the room when I came into pharmaceutical NIR, many years ago. I thought I was alone, then I heard this fellow, but you were wonderful in "Jurassic Park," by the way.

And, but as Ken says, and he probably predates virtually everybody in this room in terms of looking at something like near infrared and pharmaceuticals, that we don't know. We measure, we hope, we guess, we do a Carl Fisher and hope that the chemicals don't react with anything in there and we assume that we're doing a lot of things. But if we use the PAT as a monitoring tool to begin with and then start filtering it--and, right, we are sensitive, we may see things we

haven't seen before. There may have been changes we had--we couldn't detect before. And we'll see this and say, hey, it's subtle, but when this changes our product goes good, bad, or indifferent.

So before we worry about validating them as a control, let's see if we can get the information--because there's a difference between data and information. I once went to a place, and I noticed that they were doing the room temperature and relative humidity in every room and they had two people in the company doing nothing but changing these things. And I said, what do you do with this? And, basically, they stored it. They never changed anything due to it. They never tried to get dehumidifiers--I said, that's a waste of time, I said, it's numbers, it doesn't mean anything.

We may find that out--we may find out we are almost doing as much as we need to do right now, a moisture on a granulation and a content uniformity--you know, we automate those things and we might wind up with excellent procedures. We won't know until we actually try some measurements along the way and, again, up front, you don't know what's necessary and what's efficient. As I used

to tell the kids, you know, put the number down from the bottles, everything that's on the label, copy down. If it turns out it's not important, you just filled up some pages. If it was important and you don't have it, we'll never know where we went wrong.

But from this, we can then start design of experiment. If we can hold everything within range and vary one thing at a time, now we can do a very controlled scientific experiment and understand what's important. And we may wind up throwing a lot out and say these have absolutely no control, these are the three things we need to monitor and we have process control. We can't go up front and say let's just take everything in at once and validate it.

MR. LEIPER: I think the point that Joe made was a good one, we've actually lived in this area for an awful long time that things have been moving on, et cetera. and this is going to be no different, but our ship anchor is actually the specification that it would be tested to in the marketplace and our stability data. Because, you know, we've got--we're not going to stop stability testing at all. You know, so we're

bracketing--we're bracketing this, anyway, so as it's moving along--I think that, you know, there's a lot of good reference data that we're generating.

But I think that the difference is, it's as Emil said, and I think someone else said--it's--the testing that we do just now is just data because it doesn't necessarily correlate with our processes. It's only if that data has got that information content that holds process data that we can actually do the kinds of things that Jerry was talking about.

And then, when you move on from that, as we build that upper--not just within processes, but across processes, we begin to build up knowledge bases of approaches to formulation to work and tend to be reliable and we can--we can begin to become far more efficient at taking these things forward, so it's about data, it's about information, it's about knowledge.

And the last thing that we need is just that little bit at the top of this triangle, it's called wisdom. And that's to use it appropriately. And that requires pragmatism that I think Art refers to. Most of the time I've had his acquaintance and he's been guiding us in

these--it's a wisdom to use that properly and not just get bogged down with where we are today and the problems that we might have in the future. We're going to have problems in the future, but they're not going to be as big as some of the problems that we're facing today.

MR. CHISHOLM: Talking about dates and information, I was in Dublin about four weeks ago and they built a brand-new car park--now all the big neon signs all computer controlled, and that sign said nearly full. Now that's a completely useless bit of information, when you think about it, isn't it, for a driver? The number of spaces that's left is useful information, but nearly full, that's pretty ridiculous, really.

And I think there's an awful lot about what we do and the pharmaceutical industry's a bit like the nearly full concept. When I look at some of the things that I've seen registered in the past, by us, by other companies, they use--yeah, I can't really say us, because this is being recorded. Using five different methods to measure the same thing and registering things like that. And I really cannot see the point in that kind of approach.

But I think if I was to take a view of where are, we've got to start somewhere and I think because we're all children, really, at this game and there isn't that much experience built up, you've got to start, as I've said already, correlation to existing methods, et cetera, et cetera, to build up a confidence.

Gradually, as you move along, you'll realize that when you're controlling your process all your tablets are actually in spec, because you're looking at them statistically and you realize that that variable blend time you've got in there, which is accompanied by a certain algorithm is actually relevant and you can say that because you have all this evidence to prove it. And gradually looking at the spectra and a blend looking through a window will become the accepted primary method because people will know how to do it and it will have the same sort of background as HPLCs have for 20 years or whatever.

And I think you've got to approach it that way. You've got to learn to run--sorry, to crawl, before you can walk, before you can run. So, let's just be a little bit careful and take it nice and easy because there are a lot of goals to go for

here. And, eventually, we will have methods that will become primary in their own right, which at the moment are certainly inferential and secondary.

DR. KIBBE: We have to do this again tomorrow. And I know what happens, at least someone at my age, if I sleep on something, I have to start all over again from scratch the next day.

But what I really think we've come away, at least coming to some kind of consensus that, first that the Agency needs only provide the general guidelines and the acceptability or the understanding that we're going to accept good solid data. You've got it, we're happy.

I think we need to have some more concrete information for us to look at as a group and debate to come with or refine what our guidance is going to be to the Agency. And because there are people here who seem to have their mind firmly wrapped around some of these concepts, what I was going to ask is this evening while you're dining and, maybe, watching a rerun of "Jurassic Park," that you do some things for us. And so, if you wouldn't mind writing a three or four sentence preamble that lays out validation of process analytical tools or technology in a general sense for us to look at.

And if Jerry would--he did such a good job of lists--I love his lists--if he could give us a working list, not complete and exhaustive, but a working list that we could suggest to the Agency as suggested things for the companies to look at as they go about validating both the process and their control mechanism or their technology, that would be a good place to start and then, I would wonder if there is any other aspect of it that someone would like to work on to bring to the table, so we could start to marry it all tomorrow.

Tomorrow, we're supposed to meet as a group and then break into our groups and continue our discussion and I've noticed--and I get paranoid about these kinds of things is that at some point we have to come to a consensus and prepare a summary, you see. And being good process analytical kind of person, I'd like to begin the process of preparing a summary as long in advance as we can. So, Tom, do you have any thoughts about, what, besides those two items might be added to our little gathering? I know you came up with a wonderful list of where PAT applied last time, and some other things.

MR. HALE: Yeah, I think two things

that--and I don't know where it fits in your frame that the idea of the impact of specification writing on validation is important in that categorization, perhaps.

And the other thing is the thing that we don't do right now and haven't talked about is this idea of batch versus continuous processes because they're treated differently. And it gets back to the control and all that stuff, but it's not a--it's not a current validation concept that's widely in practice but it's the natural result of some of these things that come down the road.

DR. KIBBE: So, perhaps, you said you had some of your thoughts in hard copy back at your office. We could throw that into the pot, and then we have a wonderful assistant here.

MR. D'SA: I had a question for Jerry. You know, you mentioned about this multivariate calibration for continuous closed-loop--the ASTM criteria? Because that would be worth reviewing.

DR. WORKMAN: That's E165500, I don't have a copy with me, but I do have a--I do have a lot of the information .

MR. D'SA: Because some of the criteria that was used in that--in those multivariate

calibration, especially for the criteria used to validate the instrument, itself, and then the criteria used for validation of the instrument for the intended use that maybe the guidance wants to tackle.

DR. WORKMAN: Okay, I can provide that at a later time or some of the information.

DR. KIBBE: We have a laptop tomorrow that we can--we not me, we, that is the--my father used it on me all the time when I was growing up. It's the we--we are going to clean the car, that didn't mean he, that meant me. So, I've learned to say that over and over again. We meaning you so that when we have these thoughts from our colleagues we could put them up on a projector and be able to see them and--all right, and I think that would really help us a lot because we're going to eventually have a summary made up of that kind of information that we'll share with the larger group.

MR. CHISHOLM: Can I make a suggestion?

DR. KIBBE: Yes, please, make suggestions.

MR. CHISHOLM: I think that something needs to be in here about the general principles that you want to be adopted and when we did the definition early on, we used the word timely, which

I interpret as partly meaning statistically. So we have to take things like that into account, I think. Are we talking about statistical monitoring? Things like that, I think, have to go in the gate, but I think they're very relevant from a validation viewpoint. Because if you're actually monitoring throughout a batch, you're in a far safer position and you're doing it on a statistical basis than someone who's not doing that and your whole set of validation criteria might, therefore, be different. So I think we have to--

DR. KIBBE: So, those are two points you're going to bring with you tomorrow, right? Don't you love this--it's wonderful. The power of the chair. I've always wanted to be a chair in charge of brilliant people and I've managed to get it and it's just--it's going to my head, I can't believe--go ahead, Jerry.

DR. WORKMAN: There's one thing that really bothers me, still. There's more than one, but I'll just mention one. A lot of the discussion seemed to be that the assumption was made that all these great sensors are out there that you just plug in and they give great numbers. And, of course, that's not true. But let's say if it

was--the problem I'm having in the thought process is--a protocol on how to use the information. You have all these great sensors, they're working, they're providing the information. What kind of a protocol or procedure or recommendation is in place on how to use that information. There's an information glut, they're can be. So how--

MR. HALE: I think that gets down to some sort of categorization or rationalization of how you're going to use the sensors. We add sensors--if only the process of adding sensors is what PAT means, we do that already. There's not a lot of difference except, perhaps, in complexity between a thermocouple and a NIR/IR, it's how you use it.

You can look at fluid-bed drying with thermocouple and air flow in a nice thermodynamic model and control it just as well as you can with a NIR/IR sensor, you just happen to measure different things and do it differently. So I think it gets back in the case of validation here of how you're specifically going to use the information.

DR. KIBBE: And also it gets back to what do you accept as a usable output. And when we talked last time about fingerprinting and the image

of three-dimensional graph made from all that data and whether that image is superimposable or similar to, rather than looking at discrete data. And there's times when, if you go back to the days when I first learned how to formulate and hardness was the snap of the tablet in your ear when you snapped it, and now we have very sophisticated equipment that might not even get as good as some of the old formulators could at getting it right. So, you're right and I don't know the best way to approach that. But I know that we have to recognize that we're going to be swamped with data and we have to recognize there has to be a way of looking at that as a pattern instead of a datapoint.

And I'm hoping that information technology in the form of computational power is going to come parallel to where we're going with our sensors and that at some point that computational power will allow us to look at a sea of data at a reasonable time frame and decide whether the pattern is like the pattern was when the process was running well. And, therefore, we will continue to march because the pattern is correct. It's kind of like recognizing a rose the next rose you see, if it looks like a rose, it's a healthy rose, we keep

going. And computational power will get there and then if we're lucky, around about 2015 they won't need us, the computational power will have passed us and they'll just tell us what we've got.

DR. WORKMAN: So, is it a goal to try to come up with some discussion, at least on how we--how the information will be used from these sensors?

MR. LEIPER: I certainly agree with Jerry, I think it's a goal. I think that the problem that we're in just now is that the data that we're generating, we can't actually correlate it with process performance or product quality. That's where we happen to be now, and we've got to move on and say, okay, other sensors might give us more information-rich data and it's going to be an integrated procedure. I--and I don't think that we're going to move from where we are now into tremendous information overload because I don't think that we can make that step change.

DR. WOLD: Just one thing more that I think we need to have in the validation and that is that the company should specify the infrastructure into which he puts this and show that it is reliable in some way because you can have the most

beautiful equipment and if you can't take care of the data, store them and show them back in a reliably way, it's worth very little. And, also, the preparedness for things going down. That was discussed before, redundancy, some way of either diagnostics showing that the instrument will work for another day with high probability and detect when it's going down. So you are prepared for problems with the equipment and because with very multidimensional equipment you'll get into more serious problems when it goes down than with individual things.

DR. KIBBE: I think Jerry's point and your point are very well taken. And we need to have something in there that says at a minimum that we recognize that these are problems and that the company should have a way that they intend to approach those problems. I mean, we can't tell them how to store their data, but if they don't have a method, we're a little worried.

Anybody else have anything else, because I think we're at a stage where we can now, cogitate, modulate, ruminate if you're an herbivore and think about what we've done, and then tomorrow come back and put together something that I think might be

useful for the Agency to move forward with.

DR. MARK: One think that I'm concerned about, Jerry, one part of what Jerry said and maybe the Agency can address it, because when I got involved with this in my work with Gary Ritchie in Purdue, we'd been working together on doing NIR for quite a while. And it started--one day he brought up the question of validation, which I'd never been involved with before. And we started talking about it a little bit. And I said, well, Gary, and Gary showed up and he can verify what I said, maybe he can even actually say it better than I can re--you know, rephrase his words.

I said to him, Gary, suppose, you know, we were to somehow get a calibration model, this for NIR, suppose we get a calibration model handed down by God so we know it's the right model for this stuff. And we went through all the validation exercises and we were able to show that this model, you know, passed perfectly, it was accurate, and it was linear and it was robust and everything else that the analysis had to be. Would the FDA accept it? That if we didn't, you know, make some kind of--you know, that we just, you know, did it from the data somehow, you know by magic or whatever you

want. And he said, no. He said the Agency wouldn't accept it and the reason the Agency wouldn't accept it is because we would not have shown a causal relation between the known chemistry and physics and spectroscopy and what we were doing. You know, essentially, what Jerry was calling was in a black box, okay. We would not have shown a causal relation inside that black box, okay, it's an empty space there.

And, according to Gary, you know, and like I say, I may not be saying it right and maybe I'm not understanding it right, and maybe the FDA has, you know, a different view and what I'm saying isn't correct. And maybe FDA can address this a little bit now, to us. But he said the Agency wouldn't accept it for that reason. So, you know, the black box approach, as I understand it would not be satisfactory as of right now. Now, maybe as a result of these meetings and so forth, you know, it might be the situation now, maybe the Agency might change it's policy with regard to that--that if a, you know, it was completely validated, we could get by without the causal relation in some of these cases, but right now the understanding is that it would not be acceptable, so, that's a hole,

I think in what we're doing here, which one way or another needs filled in.

DR. KIBBE: Joe, you or me?

MR. FAMULARE: Oh, I would just say we're here trying to understand the question fully, I think would be the fairest way to answer that. You may have some wisdom you want to shed before I make an attempt.

DR. KIBBE: Well, I mean, cause and effect relationships are few and far between. Correlation that's reliable and predictable and one predicts the outcome of the other and vice versa is about as good as I think we're going to get with most of these measures. To truly understand the cause and effect, then we have to understand end Bane physics and a number of black holes in the universe and a lot of other things that might not apply.

I think what Jerry's saying is very true. If we have a reasonably tightly defined system and even if we don't know every little change in the blend dynamics within the system, if we have good correlation between two measures and they predict somehow the uniformity of the outcome, I think we're going to have to live with that.

MR. FAMULARE: I think we live with a

whole lot less today.

MR. LEIPER: I'll second t.

DR. KIBBE: You can only elaborate if you go to a microphone.

DR. ANDERSON: While Gary comes up to the mike, a comment on the whole black box idea. Black boxes are validatable, but validating a black box is problematic because you don't know precisely how to challenge that box. You don't know what the black box is susceptible to and you don't know how it is that what can go on in your process that you didn't account for early on that can change and affect you. So the less of a black box it is, the better, but that's not to say that a black box is invalidatable.

MR. RITCHIE: Yeah, along the lines of what Carl just stated and where Howard was going, what I was really trying to pinpoint in saying that here is an equation that arrived on my desk that says that this process does a certain thing. And that I could take that equation and measure that process repeatedly, the problem is I don't know where the equation comes from. How many parameters did I measure to come up with that equation. And it's not good enough for me to accept that, you

know, 3 wavelengths or 3 factors explains what that process is doing and then I can take those 3 wavelengths back again and cough up a result.

I can't--I never could accept that, unless I could show that there was a measure of specificity or that I was repeating a result due to the combinations of two or more factors and I could do that over and over and over again and know, maybe I don't know every little molecular aspect of, let's say the powder blending, or fluid pumping, but I know that every time I do it, no matter whether it's 2 o'clock in the morning or 2 o'clock in the evening, that those two wavelengths accurately predict.

There is a measure of correlation. Now, whether I can say that there's cause and effect due to the physics and what not, I don't know to what level we have to go. I imagine Svante would be able to help me out with really what we're doing when we take those factors or when we take those wavelengths. I don't believe we're looking at physics, but I know that there is a measure of confidence. And that's really what I'm trying to get at. I don't know if I made it worse or better.

I think that's what the Agency's looking

for from us is when we come to them--what is the confidence level? Where's the repeatability? What is it that you're saying this equation is doing?

DR. KIBBE: Thank you.

DR. WORKMAN: Well, before Svante addresses it, I was going to say something. Of course, if you treat it as a black box, you can look at standard samples--at one or many standard samples and determine if the black box is doing exactly what you think it's doing and what you said it was doing and what it originally was doing. So you can, you know, determine if that is functional.

And then when--if you look at full spectral data or full chromatographic data you can compare that shape and see if that's within the calibration space of the shapes that you've looked at before. If it's outside of that then, obviously, you have, you know, a problem. If it's inside of that, then you're interpolating if it's done properly and you know that you have some confidence in that result. That's my.

DR. WOLD: Yes, about this little black box. I think that it's two different issues. One is to say, as Jerry, that we validate it as a black box and that's a very nice thing to do because then

we don't make any assumptions--we change things we can change and we see that it reacts in the way we want it to react. That doesn't mean that we believe it is a black box.

Now, I don't think that anyone here in the room is willing to accept a PAT or anything else, if we don't think that it is based on scientific principles and built according to our best scientific understanding. Then we know how to deal with it. And we know what to expect from it. So we don't have black boxes. But when we validate them it is at advantage to deal with them as if it were a block box. That's two different things.

DR. KIBBE: Thank you.

Go ahead, Tom.

MR. HALE: Can I ask a logistics issue?

DR. KIBBE: Yes, you can ask a logistics issue.

MR. HALE: On our homework--

DR. KIBBE: Yes.

MR. HALE: --if we bring it electronically, is that okay?

[Inaudible comment off microphone.]

DR. KIBBE: The answer is yes. They're working out the logistics of the logistics. Yes,

if we bring it in electronically, he'll be able to work it in somehow, and you have a question about logistics.

DR. LO: I just want to say, anybody that wants to do this, I'd prefer electronic to my typing which is two fingers. So, please, electronics.

DR. KIBBE: Tomorrow, we are supposed to be called to order at 8:00 a.m. by Dr. Layloff, who will not be here, but I will and I will usurp his chairman's authority and call us to order tomorrow. And then, we'll be making the regional--Kathleen will make her statements, you know, how she says that none of us are biased because we don't know anyone else in the world. And then we'll go into our working groups and we'll continue to do this until we get close to lunch and then we'll be able to report back to the group. So, have a good evening folks and we'll look forward to tomorrow.

[Whereupon, at 4:47 p.m., the Subcommittee adjourned to reconvene at 8:00 a.m., Thursday, June 13, 2002.]

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