this is another suitable use argument.

DR. TIMMERMANS: Agreed.

DR. KIBBE: How's that?

MR. LEIPER: I think there is an assumption there that the validated method exists for a regulatory parameter. But does it actually meet the real need? You know, we haven't actually--there's nothing there that says it meets the real need. A real need.

MS. SEKULIC: Maybe we can provide the assumption that if an original method already exists, that a need has been identified. Maybe.

MR. LEIPER: Well, I think that that's the--

DR. KIBBE: That's the hope.

MR. LEIPER: That's the starting point. You know, does it actually meet the real need?

DR. MILLER: It seems to me if you have a new method, it would probably need to be validated essentially to the same extent that the original method was also. Now, the values from the old method could be used for those validation parameters where it's appropriate, such as accuracy, perhaps. But the other things, such as, you know, precision, which don't necessarily depend

on the values obtained from the other method would probably have to be validated as though it were a completely new method anyway.

DR. NASR: I think we have to distinguish between using information or data from the old method to validate the new method, and using the same validation criteria for the new method, I think we have to make that distinction. The method should be suitable for the intended use. We can use the old method to generate data that we can utilize in validating the new method.

MR. COOLEY: I think that's a very important point to make. We utilize on-line HPLC to monitor and automatically cut purification columns, and the on-line assay has a large bias compared to laboratory assay. But the bottom line is we can set criteria that we can use information from that instrument to do process control with, and I can produce mainstream cuts that meet the forward processing criteria every time, even though there's a large offset between that--for a large bias between that assay and the lab assay. So it meets its intended use every time.

DR. KIBBE: So have we got that in a simple correction, or do we need more words? We're

good? Let's try another one.

DR. TIMMERMANS: Well, the only thing that was missing here, we talked about the range--or are we--

DR. KIBBE: Different question. We're going to be home on the range soon. How to handle the validation method for a non-regulatory parameter.

We don't want to do that, right? We just don't want to--if it's not regulated, we don't want to know about it?

DR. WOLD: We get into a problem here. We have said that if we want to use measurements--measure during the process instead of making an end analysis, then we may decrease the end analysis a lot or maybe even get rid of it. If we just use methods corresponding to what we do today, but substitute for PAT everywhere and use them for end analysis and so forth, then we will not be able to move things earlier in the process, and we're in the same way as before. So we have to in some way have a mechanism to incorporate also measuring at new places earlier with new methods, and that will automatically be new. It was because it doesn't exist in the regulated method now for

that, by definition. So we have to--and they have to be validated; otherwise, if AstraZeneca or somebody comes and wants to apply for a new drug and they say we do this now with new methodology and whatever, then we have to have validation demands on those.

DR. KIBBE: So the statement is correct the way it is; we don't have to change it? If you're going to put in a method--a process assessment technique, you have to validate it no matter who wants you to put it in. If you want to put it in for yourself or the agency comes and insists or someone--it doesn't matter. You really have to validate what you're doing. Generally accepted? Yes? No?

DR. WOLD: If you are going to use it for on-line quality control, of course, then you have to validate. But we have also said that for research use and for process investigation and so forth, you are allowed to put in methods just for, say, process studying purposes. And there we can't have the same demands on validation, or you don't need any validation at all, because part of it may be to investigate that this measurement works. And you have to be allowed to do that.

DR. KIBBE: It says "appropriate validation," right?

DR. C. ANDERSON: Can we address your comment by changing the question a little bit, by making the question to say validation of PAT methods for release criteria or for real production? That's where I hear you driving.

DR. WOLD: They are going to be used for release.

DR. C. ANDERSON: For release.

DR. WOLD: Yes. So after the question mark, put in "which will be used for release purposes."

MS. SEKULIC: Can I just suggest that we change the word "release purposes"? That has a different connotation. It means end-product release in a lot of cases. Maybe we want to change it to "decisionmaking"?

DR. C. ANDERSON: In-process criterion?

MS. SEKULIC: Yes.

DR. C. ANDERSON: What is the word that wants to be used there?

DR. KIBBE: Is "decisionmaking" okay? Because it's pretty general. Yes, let's go...

DR. WORKMAN: Might we add to the second

italicized point "are allowed for research purposes," something...something that reflects that they don't need to be validated, they're allowed for research purposes?

MR. COOLEY: Could you explain the example you guys were discussing there when you're talking about a non-regulatory parameter? Because I'm having difficulty understanding what that might be.

DR. TIMMERMANS: I was trying to remember a specific--whether we did actually discuss a specific example. But, for example, a crystallization onset, okay, process parameter, we measure, we might want to measure the concentrations of various components in the solution or the concentrations of the various crystal forms as they're being formed.

Now, that's not a regulatory parameter. It's something that we use to make a decision as to whether we go forward with that crystallization process, but it's not filed with the FDA. So that would be an example of a non-regulatory process analytical technology that we would use and would want to implement.

MR. COOLEY: Wouldn't that still be considered GMP, though?

DR. TIMMERMANS: It would be considered GMP, correct.

MR. COOLEY: But your definition of GMP is not necessarily that it's a regulatory parameter?

DR. TIMMERMANS: When I talk about a regulatory parameter, it's something that is filed.

MR. COOLEY: In the NDA.

DR. TIMMERMANS: In the NDA.

MR. COOLEY: Okay.

MR. CHIBWE: So is that just for information only? I mean, just collecting the information just for information only?

DR. TIMMERMANS: No. We may make a decision off of the measurement.

MR. FAMULARE: In my mind, I wouldn't call that a non-regulatory parameter. Maybe a non-filed parameter. But I don't see that--to me, a non-regulatory parameter may be some function of running the machine--or the equipment to use the least amount of electricity or something of that nature that you may want to monitor through some means.

MR. ELLSWORTH: Process optimization parameters, not necessarily regulatory. That's what I see from that.

MR. COOLEY: I can give you an example of that where we--you know, biotech processes may have ultra-filtration filters or a centrifuge, and the waste stream we monitor in both of those with optical density measurements to keep from losing product. So it's a business decision, but it has nothing to do with product quality. But that's a good example. We still validate that in the same way as we do our GMP sensors.

DR. TIMMERMANS: I agree with Joe that in this case the term "non-regulatory" was probably a poor choice of words.

DR. KIBBE: Go ahead.

DR. WOLD: I think we have to specify more the decisionmaking about what, because anything we use for some kind of decision, it should be a decision about the product or the process or something like that.

MS. SEKULIC: But both of those fall into the same regulatory scrutiny bucket, so I guess I don't see the distinction. But I agree, it covers both cases. Because as soon as--as we've just discussed, as soon as you start taking action based upon, you know, a method, a data point, a piece of information, then it's decisionmaking.

DR. WOLD: Yes, but we do other decisions. We say, oh, I like this, and I want--in the research we make decisions, too. We say this works.

MS. SEKULIC: Yes, I see this is covering the validation component, and the only suggestion I was going to make was to make a distinction between the method development or the learning phase. I'm assuming that this takes off from when we actually have established what it is that we want to monitor and how we want to monitor it. Therefore, I have a method; I'm now looking at validating that method.

DR. KIBBE: Are we ready to move?

MS. SEKULIC: The "non-regulatory," do we want to fix that before we go ahead? Maybe "non-filed"?

DR. KIBBE: Is that better? Remember that we're not writing regulation here. We're talking about issues that eventually will go into a guideline. We need to do as good a job as we can, but not beat the horse to death here.

MR. FAMULARE: The only suggestion I could make--I don't know if "non-filed" does it for me, either. You may want to still validate a method because it's necessary for GMP, so that I think

we're--I don't know what--I'm not quite sure of the purpose in this example, but maybe you're trying to look at something that's not that critical versus something that is more critical to validate. And I think the degree of validation should hinge off how critical that particular process or parameter is.

DR. C. ANDERSON: Isn't that what the answer is saying there, Joe, that even though this may be a non-filed--or however one wishes to say it--a less than critical parameter in the manufacturing? As for other analytical methods, use scientific judgment to develop appropriate validation? So what we're saying is use validation appropriate--

MR. FAMULARE: Right. In the further statements. I don't know what the distinction is in that example. You could have a critical thing that isn't filed.

DR. NASR: What if we use "non-critical"? How to handle validation of method for non-critical parameters?

MR. FAMULARE: It's not critical, but you use it to make a decision.

[Inaudible comment off microphone.]

MR. FAMULARE: Well, that may be the

answer, too. Maybe--well, not to measure it, but--I don't know, I just--I don't know what it does for you, that first example. But--

DR. WORKMAN: Could we make that statement broader? The parameter that will be used for learning or decisionmaking? Because even if you've established the process, there may be other things that you can learn for optimization, especially economic-related. So...

MR. CHIBWE: I don't know if you really need to do formal validation for some process that's going to be filed. I'm just wondering if that's necessary to do formal validation. A good example is it's really fractured during research papers. You don't necessarily validate that. I mean, you're going to have your polymers, maybe two, three different polymers you could distinguish. But we usually don't go to the extent of doing any validation for the method. So I don't even know if validation here is going to apply, other than you making sure that your parameter measurement is robust enough, just for information only within the company.

MR. ELLSWORTH: I have a question and maybe a comment. I'm not absolutely sure why we

are even dealing with or trying to deal with something that may not be a regulatory requirement in an FDA guidance. We usually don't speak to thinks that deal with process optimization. So if it's not--if it doesn't have a regulatory purpose, then really why are we dealing with it in this guidance? I guess that's my question.

DR. C. ANDERSON: As a user, I would like to see some acknowledgment that these technologies may be used for purposes beyond direct regulation. I think it goes to the safe harbor idea, to formalize some of those ideas a little bit, that we are committing as companies to do validation and do it properly, but at the same time looking for sort of the exemption to be able to use this as an information-only-type article.

MR. FAMULARE: That may be okay. I'd have to think about that. But, still, the distinction of filed or non-filed does nothing for me. At least, you know, when FDA sits down to write the guidance, that--I'd probably remove that term right off the bat.

MR. CHIBWE: I really don't think that it's appropriate to do validation for information only. It's information only--if it's during the

safe harbor, you really don't need to do any formal validation until you reach a point where you say you're going to implement that, your system is optimized, and the FDA is definitely going to look at that. That's when you're going to go to the formal validation. So I really don't think this is an appropriate question to address at this point for this purpose.

MS. SEKULIC: I'm just wondering in reading the questions--and I certainly don't want to put words in Mark's mouth, but was it possible that the distinction between the two questions is that one scenario, the first question on the hard copy, was where you already had a method in existence that you could correlate to, whereas the second part was where you don't necessarily have an analytical laboratory method in place, and so you're monitoring, you learn something, and you're in that situation, how do you validate and go forward? I'm just trying to understand the questions, because I think I tend to agree, we're going to be held to the same level of scrutiny no matter, you know, whether it's a GMP question or a regulatory filed method. And as scientists we're probably going to validate the thing, anyway, just

to get confidence that, you know, the sensors and the methodology is giving us the appropriate information anyway. So, I mean, I think that drops that sort of whole question unless the intent was to probe, if I see something on my process sensor but I don't have a direct laboratory method, what do I do then? I don't know. You might want to comment.

DR. TIMMERMANS: Yes, again, you know, this is a synopsis of a discussion that we've had for a whole day, and I truly did not expect Ajaz to bring this up here and start this as a discussion point for, you know, what should be included into the guidance.

In this specific case, I think as I mentioned before, we were talking about parameters which were not necessarily in our filings. We might or might not fall under GMP scrutiny that could be used for multiple purposes, you know, for process learning, for increased understanding of our processes to provide us a pathway, you know, to gain the process understanding, and, you know, that's really the context that this was discussed in. I'm not sure--I agree with Carl's point that, you know, the guidance should preferably provide

some type of information or position on how these methods should be used, but agree also with Doug that, you know, for non-regulated, non-GMP, non-filed methods, you know, how can you provide guidance. You can't.

DR. KIBBE: Is Merck prepared to claim proprietary information and have us move this because it's secret and we shouldn't talk about it?

[Laughter.]

MR. LEIPER: I think that Merck would be glad that we're confusing ourselves with it.

[Laughter.]

MR. RITCHIE: Can I add, with respect to what Carl said, I think I'm having a problem with giving the industry the right to reserve the use of data for investigational use or development purposes with never the intention of having that show up a filing.

I also need to be able to defend the use of that measurement for someone who inside, you know, looks at it and says, What are you doing with this? Why haven't I seen it?

So for instructional purposes, I think you need to straighten out the usage, because both--the investigator needs to know the difference between a

reported value that's used for development or investigational use to learn about the process versus the final one that's going to be reported. I don't know if that straightens it out, but that's what I think is going on.

DR. KIBBE: Are we comfortable with what we've done here? Do we have enough confusion added to the pot to go on to the next one and try confusing that one?

DR. NASR: Did we decide to drop the question or what?

DR. KIBBE: We haven't thrown anything out. We were looking at this to see if we could enlighten Ajaz, because he already has this list. And if we can't make it a more enlightened statement, we're going to let him live with what he's got. How's that?

I see someone with a finger on the button. Go.

DR. HUSSAIN: Well, I think you talked about why I brought that list here. In a sense, I think it was prudent of me since we had that discussion in sort of a closed session, and I didn't want that to sort of remain in a closed session, and so that was the reason to bring those

questions here. It's your choice whether you want to drop that question or not. So that's fine with me.

DR. C. ANDERSON: I think we've substantially modified the question by taking out the whole non-filed, non--all the "non" stuff out of there. The "non" sense, as it were.

[Laughter.]

DR. C. ANDERSON: I think the question as it stands now bears looking at and deciding whether, as it's written now, if it makes sense.

DR. WORKMAN: To me it makes sense, for instructional purposes.

MR. SILVANS: Can we use not only for process monitoring but also for process setup? Because sometimes we use, for example, NIR for--see the flowability and particle size, and from these physical properties we set up the filling machine, for example, as a practical use.

DR. KIBBE: What word would you add?

MR. SILVANS: Say method for process monitoring or process setup.

DR. KIBBE: What was the word?

MR. SILVANS: Instead to say for process monitoring, that's okay, but we can use for process

setup.

DR. KIBBE: Setup.

MR. SILVANS: Yes. Before starting your operations in the morning, you set up the machines on the basis of the results you have.

DR. KIBBE: Okay? All right. I've got 11 o'clock, and we've got several of these, and we're having so much fun with them. We'll move on to the next one.

Number 3, when and how do you validate. I think how is up to the process--we've had lengthy discussions about letting people use a reasonable scientific approach to validating based on the instrument in this process or system you're trying to validate. I think more importantly is when, and being naive and being an academic, I always go with you validate when you want to have faith in the answers you're getting, you don't validate when you don't care.

MR. COOLEY: Art, I think you make a valid point. Validation--there's two drivers for validation. One is for compliance and regulatory, and the other is for business reasons. And it doesn't make a lot of sense to put a sensor into a process and not do some type of validation to

ensure that the data you're getting out of it means something. But obviously there's many, many levels of validation that you would be dealing with there.

DR. KIBBE: I'm glad we're talking about making valid points in a validation discussion.

MR. COOLEY: I have a question on the first point. Are you inferring there that you would not validate at all? It says calibrate PAT method for use in pilot plant--or these sequential steps that you're talking about you would go through.

DR. TIMMERMANS: Correct.

MR. COOLEY: Okay.

DR. TIMMERMANS: You know, in order for you to be able to validate the method, you first need to calibrate it. So what would be your first step in the process?

MR. COOLEY: Okay. I didn't know if those were multiple-choice questions as to which you would do or whether they were sequential.

DR. KIBBE: We're okay? We're going to go to the next one. No one's going to jump in here and object? All right. Go.

[Pause.]

DR. KIBBE: I think this kind of implies a

concern that people have. If you put one sensor on a blender and it starts to screw up, does that mean you have to kill the whole blend because your sensor is screwing up? Or is there a way to nest our process technology so that if one monitoring system is going bad on you, it doesn't mean that you have to kill the whole run, or whatever? I think that's where we're--I'm not putting words in Merck's mouth, but I think that's where they're going with that. How do we want to handle that? Go ahead.

DR. WOLD: Well, again, I'm not speaking for Merck here, but I think that remembering the business interest, I mean, nobody should put just one sensor on to measure just one thing. You always need redundancy, and that comes from the process people. If you have good process people, they will ensure that, and you don't need to regulate that because the business interest is to not let this happen.

DR. TIMMERMANS: I think Ajaz discussed this in part yesterday in his presentation as well when he was talking about, you know, overlapping systems and several layers of redundancy being built into the process. So I think that that in

part addresses this question or this issue.

DR. KIBBE: I wonder whether the concept of robustness of our testing method or in-process control method or technology ought to enter into this. If you have a very robust system, then there's less need to do lots of redundancies. If you have one that fails on you every two weeks, you should be doing something different. That is truly a business decision.

DR. MARK: The question here kind of reminds me of something we started talking about yesterday a couple of times and never really got all the way through it. The question came up yesterday, if you have a continuous process, it's running along okay, and then all of a sudden something happens to it, it goes bad, then what do you do? And we never really followed through because the second part to that question, which probably also--you know, that needs a discussion in itself. The second part of the question is now you've fixed the problem--maybe, let's say, it's an hour later. You've fixed the problem, and then what do you do? Is it still--if your sensor and process are in control again, the sensor's been fixed, whatever the problem is has been fixed, and

now the process can run along and be measured and be kept in control, can you then go ahead and continue taking the product and eventually releasing it?

These are two related but separate questions which we never really followed through the discussion yesterday. This question seemed to be addressing it also.

MR. MADSEN: And, again, I think it makes a big difference whether this is a sensor that's used to control the process or just to monitor the process.

DR. KIBBE: My own personal temptation is redundant systems, so that if I have a monitor that goes down, then I'm not left wondering where the thing is going. But, you know, I don't spend the money.

DR. C. ANDERSON: In general with this sort of question--

DR. MARK: I was going to say, that's okay if it's the sensor went bad. What if the process went bad and the sensor did its job and caught it? You know, it doesn't remove it entirely, I think.

DR. C. ANDERSON: My comment actually goes very nicely to what Howard was just saying, I

think. It's the company's responsibility to have procedures in place that address these, and I think from the level of the guidance, the guidance needs to specify that procedures need to be in place. I don't think it's our job to prescribe those procedures. I think it's the individual company's job to come up with reasonable procedures to address this type of contingency.

MR. LEIPER: I think that the other thing that's important is that we're actually reinventing the wheel to some extent here, because many industries actually run continuous processes and they do have contingency plans for these particular issues, to such an extent that their processes are so hazardous that if they did go out of control, they'd be blown up or something like that.

So I think rather than debate it all here, the answer is to go out to some of these industries, find out how they handle it, and see how much of it can be imported into our strategies, because we don't have this experience. None of us around the table have actually got this experience.

DR. CIURCZAK: Well, in a way, if you look at a small enough part, the same concept if you get in a short enough area, the Earth is flat. If

you're running tablets from a single granulation and it takes three days to make the batch, so those three days it's a continuous process. And you've got your first million and a half tablets, then 10,000 go bad, you fix whatever it is, and then the rest that are good, is it legal to throw away that little piece in the middle and sell the rest of the batch? That's basically what Howard's saying. How do you judge that?

DR. KIBBE: Anybody else? I think rather than putting up there the statement that we need a robust sensor, what we really need is that the company needs to develop a contingency plan for failures in the process. And they have contingency plans now for failures in the process. It's just we now have a different method of monitoring the process, and so the contingency plan has to take that into account.

DR. WORKMAN: Might I add that it is implicit in here, but some of these other industries that Ken was talking about are monitoring the monitor all the time, so they know whether it's the monitor or the process. That's what you--that's part of the plan.

MR. CHIBWE: I don't know if we should use

the word "non-regulatory" or probably just say "for information only parameters." Number 1 there. Because the whole environment is a regulatory environment, so I don't know if we could specify non-regulatory parameter. Maybe you could just use the word "for information only parameter."

DR. KIBBE: I'd be real tempted to make that one statement and get rid of regulatory, get rid of non-regulatory, get rid of--I mean, we have a parameter--if we're looking at a parameter, we must think it's important. If we're looking at things just for ha-ha's, then we're spending money for no reason at all. And so if we're looking at a parameter, then we need to have a way of making sure that the parameter is measuring something we want to measure and that we can depend on the outcome.

MR. COOLEY: Could we not do what you just mentioned earlier, Art, and just strike both of those and just say that there will be a compliance plan--I mean a contingency plan in place that--it's up to the company to determine what the appropriate contingency plan is.

DR. KIBBE: I'm with that.

DR. C. ANDERSON: I agree.

MR. LEIPER: Totally agree.

[Pause.]

MR. COOLEY: Art, Ken brought up a good point.

DR. KIBBE: He always does.

MR. COOLEY: Is this considered a GMP document? If so, do we just need to strike it out once and then initial it that we've changed it?

[Laughter.]

DR. KIBBE: We're doing it electronically, so we will have to initiate a method for electronic initialations. Okay? And so we're going to have to validate that method, and then we're going to have to monitor the initialator.

Are we ready for in-vessel?

DR. C. ANDERSON: My first suggestion is that this isn't restricted to in-vessel. There are examples I can think of that are out-of-vessel that are just normal processing things, that the only time we can gather data is while the process is running. So I guess rather than in-vessel, perhaps in-process might be a little bit more specific.

DR. KIBBE: Let me see if I've got this. PAT methods are--I don't know--in-process methods, right? So we're going to make this in-process?

In-process?

DR. C. ANDERSON: It looks very reasonable. He just changed it to "a PAT method."

DR. KIBBE: I like that.

DR. C. ANDERSON: Which seems quite reasonable.

DR. KIBBE: Are we okay with this one? You've got something? Go.

DR. WOLD: We are tying our hands here, or the process people. If we start to operate outside this optimal range, then we are actually getting data where we can compare the PAT method with the laboratory method, so you can use it for updating. So we shouldn't say that we always do this. It becomes very static.

DR. C. ANDERSON: Not necessarily. What this says to me is that if I wish to use it outside of the initial operating range, I have to revalidate to demonstrate that the extended range is appropriate.

DR. WOLD: But, I mean, we are getting data. We are saying we can collect data only from the run in process, and suddenly we start to run the process somewhere else. Now we have data, so we can compare the process at this point or in this

little range to the laboratory method. So then I agree, we should then update the model or whatever we are doing. But the way it's written here when it's operating outside this range, this is this little initial range, then we forever must use the laboratory method.

DR. C. ANDERSON: As a point of clarification, I agree with you, yes.

DR. KIBBE: Good. That's good. I'm glad you think so, too. We're ready to move on, right? Six.

That's generally the same statement. Okay. I don't think we have to do anything with it unless you want to just delete it.

Let's go to the next one, which is, I think, the last one, which is always nice.

All right. Jack, no one has anything? Okay. Well, we've done that little job.

I'm one of those people who don't like to work any more than I absolutely have to. Is there anything else that we need to discuss?

MR. COOLEY: One thing, Art. It's not a point that I don't think we've discussed the last day and a half, which is surprising. It has to do with measurement uncertainty and how that ties

into process limits, and I guess gets back into the suitability of the sensor to be used for controlling a process that is within those limits. And I don't know if that's something that should be included in this guidance document. It is something that's starting to be observed by some of the field inspectors, and I don't know if it's a good thing to capture for other companies that haven't gone through that process yet.

DR. KIBBE: You're not just talking about the Heisenberg uncertainty principle, right?

MR. COOLEY: No. No, I'm talking about, I mean, determining what the uncertainty of the method is, the total uncertainty, and in setting--and defining that in the method, and then there's kind of a consensus standard that you will have a 4:1 ratio of measurement uncertainty to the process limit, that you'll operate within that range. We really--we haven't captured anything to that level of detail, and I don't know whether that's something we should or not. It kind of gets down to you don't--obviously you don't want to have a measurement uncertainty that equals your process limits, or even comes close to that.

DR. C. ANDERSON: I agree with you

completely, but I think we are getting beyond--below, if you would, the scope of this guidance.

MR. COOLEY: Okay.

MS. SEKULIC: I'd say that probably gets covered under the appropriate for intended use consideration perhaps.

DR. MARK: There's a phrase in a couple of these questions which brings up a point which I haven't heard addressed here either, and the phrase used is "long-term maintenance." We all know that a lot of these methods--you want to have some sort of quality control on the method, that, you know, at some intervals you compare it again with your laboratory or your prior analytical method if you've calibrated it against a prior method to make sure that it's still maintaining its accuracy and so forth. And I think something should be in the guidance about how often and to what extent the ongoing quality control procedures should be applied. Probably it does not need to be as thorough as the initial validation of the method, but depending on how frequently it is, you possibly may want to have a guidance that says you'll do something minimal at weekly intervals, and

something a little more extensive at monthly intervals, and something like that. But I think there probably should be something mentioned about the question of this long-term maintenance procedure.

MS. SEKULIC: I guess I'm going to disagree. We have instrument guidelines in place that tell us how to calibrate, how to performance verify, how to do this, how to do that. If we're talking specifically about monitoring a process unit operation with a sensor that is product-dependent--it's going to be really difficult to provide a useful guidance that isn't so general that it becomes redundant, because we have, what, 50 processes, 50 products that are manufactured at any given time, each one of those will require different cycle times, different number of batches being manufactured per campaign. So depending on how you set up your sensor activity and your process monitoring activities, those may actually require--and the complexity of those, they may require different verification/sensor monitoring activity to be implemented. And that, I would also venture to say, would probably go into the method development documentation, shall we call

it.

DR. MARK: That could be. Maybe we need something as simple as to say that there shall be an ongoing long-term maintenance procedure put in place.

DR. C. ANDERSON: That was on there.

MS. SEKULIC: Yes, I thought we captured that in one of the questions.

DR. MARK: These questions just sort of assume that it's there, but it doesn't say that it should be there.

DR. NASR: I think it is a given in existing GMP environment that you have to have--maintain your equipment and you have to have all calibration and all that. I don't see anything new here.

DR. TIMMERMANS: Well, I think, Moheb, the only thing different here, and speaking from experience, if you, you know, take a specific example where you replace a KF measurement by a NIR measurement, how do you know your KF measurement is not going to drift, but it's very possible that either your spectrometer or your materials drift or your calibration drifts. So the question then is how often--and I think that that's what Howard was

coming to. How often do I need to verify that my calibration is still appropriate? And what do I need to do to verify that that's appropriate?

But I agree with Sonja that, you know, we're talking in very general terms here, and we cannot provide specific guidance. I think the only thing, as we said before, is that we have to have a long-term maintenance program in place, and the appropriateness needs to be determined, you know, at method validation.

MR. COOLEY: You think there are guidances available. The NCSL, the National Congress on Standards Labs has procedures or consensus standards that deal with PM frequency analysis and that sort of thing. You could use those.

DR. KIBBE: I want to thank everybody for all of their energy and effort. What I intend to do, if we break, is I'm going to go look through the slides we developed earlier that we all seem reasonably comfortable with, and they're going to make the basis for our team presentation after lunch. Just if anybody is interested and wants to go through them again with me, we'll stand around the young man with the computer and make sure that they're appropriate. All of this material is being

captured in electronic format so the agency will have all of it. None of what we've done is the letter of the guidance or guidelines or the law that's going to go into effect. We know that FDA staffers will get a chance to go through it again and, you know, fluff it up or tone it down or whatever.

But I think what we have attempted to do is give them some really good direction for that ultimate guidance, guidelines, and I think you've all served your companies' interests well and the interest of the public, and you've been open and honest with us, and we really do appreciate that. As a reward, you get to go to lunch early.

[Laughter.]

DR. KIBBE: And we will see you at 1 o'clock. It is our understanding that at 1 o'clock we'll have reports from the standing--or the sub-groups, and then we'll be out of here. I think Ajaz and I have estimated that you will probably be on the road at 3 o'clock if you've already checked out, or in the bar at 3 o'clock if you haven't, whichever direction you want to take your life, although I do recommend to you that you hold to the normal process limit for the consumption of

alcohol. It's one drink an hour.

[Whereupon, at 11:27 a.m., the Process and Analytical Validation Work Group was adjourned.]

AFTERNOON SESSION

[1:05 p.m.]

DR. KIBBE: In light of the wonderfully sunny, pleasant weather outside, I thought we could go ahead and get started. The presenter is always praying for rain during his presentation and not after. And so what we're hoping to do is that this rain will blow over in a couple of hours while you're stuck in here with us communing about the wonderfulness of PAT, and then you'll be able to get out in a cooler environment than you arrived in, with pleasant sunlight and a nice view of the freshly washed Gaithersburg, for those of you who have traveled here from afar.

x We're going to try to summarize the 15 efforts of the individual working groups that worked yesterday late in the day and early this morning. And I think using the power of the Chair, I'm going to get mine over with first. That will give you an idea of how much time we've left you for the other people so that we can keep things on the move. Just remember that Ajaz wants to summarize at the end, and I know Ajaz, and that's an hour and a half. So that leaves us--

[Laughter.]

DR. KIBBE: That leaves us a little time.

I was chit-chatting hoping my colleagues up here are ready. How are we?

[Laughter.]

DR. KIBBE: So, Judy, we're loading yours, and then I'll do mine, and we'll do yours, and then we have to do an equipment exchange for the training people because the training people didn't bring equipment to allow them to transfer their information. Training, non-transference of information, that sounds good. That sounds wonderful.

While he's loading, let me tell you that, first, I enjoy these meetings immensely, which only goes to prove that I have a very limited life.

[Laughter.]

DR. KIBBE: But on a more serious note, there were a number of people who worked with me yesterday and today who are both experts in their field and have courage and determination to try to move forward on something that will ultimately be a great benefit to both the industry and the general public in years to come.

I understand that some of them have some fears and trepidations about a regulatory body that

has been in the past inconsistent at times, and even punitive when necessary. But I really do appreciate their willingness to look at this in the environment that we find ourselves in now, with a regulatory body willing to go the extra mile to make the improvements in their regulated industry. This is a wonderful opportunity for all of us.

Now hopefully there is a slide behind me that says something that I can keep going from. Being a university professor, I always do things in 50-minute blocks.

The first move is, of course, to find the button to push the slide, right? Which one of these--you sure you like this one? That worked really well. Left. Left-right arrows? You're sure? Outstanding.

Well, since I've tried up-down, left-right does work. This is called validating the process. When you have four possible outcomes, you check them all and see which one actually changes the--

[Laughter.]

DR. KIBBE: We have a working definition of process analytical technologies. I keep hoping that we will somehow change analytical to assessment technologies because I think analytical

ties us in our own minds to the history of HPLC, and for those of you who are old enough to remember real titrations and gravinometric(?) measurements.

This is a working definition that will allow us to move forward. We hope that the validation guidelines will include some of the kinds of information that we include on this first slide of definitions. This is a system for the analysis and control of manufacturing process. What is the validation that we need to go into? You know, three lots and done. Ha, ha.

When we had our discussion, we recognized that this is a new way of looking at what we're doing. It's not an analysis of a snapshot. It's the continual monitoring of a process. In order to do that effectively, we have to know what the process is. If we don't know what we're monitoring, how can we expect that the results of our monitoring can be useful?

We had the discussion about validation and some background information. We have a belief that a lot of what we do doesn't correlate well with the process we're trying to monitor. We know that we have in the past used univariate measures, but we're looking at PAT and we're recognizing quite

easily that it is a multivariate analysis, and so we have to look at these things slightly differently.

We sometimes measure what we can measure, even though it is of no value to us, and not what we really need to measure. And I think we need to be more rigorous in our attempt to measure what is essential to our processes.

Measurement has not been seen as process-related in the past, and we need to change that. And we need to have--some people call it a paradigm shift. I don't think it's nearly as dramatic as a paradigm shift. But we need to think differently about how we go about maintaining quality in our products. We have to recognize that our approach is to control the process which ultimately gives us a quality outcome.

We have to understand the process, break it down into unit operations, assess the risk potential for each unit operation, design systems to manage the risk, remembering its univariate measurements are not appropriate for multivariate systems. We have to develop our systems. We have to establish proof of concept. And then we have to challenge validation.

Our objective, of course, would be to confirm the process and measurement validity in a real time across a life cycle of the process.

Some postulates that we think should be included in the guidance that would help the industry understand how to proceed, and a couple of things that came up in our discussion that is also worth nothing is that a lot of us think that we understand how to validate an individual activity or a process or an individual way of monitoring an outcome or a product. And we think that some of those understandings, especially if they're backed up with science, solid science, can be applied to understanding a PAT or a process assessment technology. But at the same time, we have to recognize that they are different, and so we're on the horns of a dilemma or a paradox as we have over here on the structure in the upper right-hand corner. And that is that we think we know how to do validation, but we think we know how to do it in a certain area or aspect. Can we apply all of those same principles to our new area or aspect or our new way of doing things? And if so, how successful can we be? And I think part of it is keeping your mind open to what you're dealing with,

which is a process and a static measurement, and realizing that we don't need to go to excruciating detail to reinvent the wheel, but we need to know that the wheel we've selected fits the car we're driving.

We have a checklist for sensor and chemometric validation which we think ought to be included in the validation guideline to give industry some sense of what we're looking at, to remind them, more than instruct them or teach them, of the things that they look for when they do a validation. And if they do it right in the past, then they can probably use these same reminders to go ahead and do it again in the next stage. So a sensor validation, software validation, and remember, when we look at PAT--and all of you have been looking at it over the last few days, if not long before that--we recognize that these systems are going to generate a tremendous amount of data. And how we manage the data is going to be equally important. How we get real information out of a sea of data is also going to be important, and how validation uses that information as well as the data that it's presented with.

Targets for validation and method types.

We have primary methods and secondary methods, and, again, this should be included in the validation guideline as a way of reminding you of the kinds of things that you think about when you go through validation now and perhaps how that can be applied to these types of systems. Analytical types, direct measurement, in the past we've looked at only active ingredient. Now, of course, we want to look at active ingredient and all the excipients simultaneously. Our general thinking should be approximately the same.

Now, interventionality--and we can't say this more often than is necessary, and that is that we're looking at multivariate, we're looking at fingerprinting a process, and hoping that the fingerprint is very instructive as to how well controlled the process is and validating on that fingerprint so we have multivariate systems.

Implementation questions. What information is needed and why? Where are the appropriate measurement points? When and how often are the measurements needed, and how is PAT provided the information to be used? And who will interpret this information? All right? All of those things have to be addressed as you begin to

add these types of technology into your processes.

There are three distinct ways of analyzing unit operations and releasing products that are being developed and manufactured. Condition one, generally the current operating scenario, the product is manufactured according to a fixed process condition set. One of the best examples, of course, we've talked about over and over again is that we set up blend in a specific piece of equipment to last a specific length of time.

When we look at in-process or PAT applied to blending, we agree that perhaps there will be an endpoint and that 15 minutes isn't the endpoint but, rather, at some point when the sensors say they have a uniform mix, that's the endpoint. And so there is some of the way we shift and the way we think about things.

Release is conducted by physical and chemical tests subsequent to manufacture. Some of the concerns that we talk about is when can PAT replace some of these end-stage release measurements, and I think we generally agree that early on, probably not, for a number of reasons. First, we think all of our QC people would go crazy if they thought they lost their job, and they would

insist on doing the study anyhow. And if they thought they were losing their job, they would stop any attempt at putting PAT in place because they wouldn't want to lose their ability to assay all these little tablets that they get. But also because there will be some uncertainty at various levels within our companies and there will be some assurances needed that what we're doing is really going to do what we want to do. And I think we had a wonderful slide, and Machiavelli told us that if we want to change something, we'll be opposed quite dramatically by people who like the way we do things already and supported only lukewarmly by those who want to--who think they might get something out of it, and so we're going to have that issue in front of us.

Product is manufactured according to a process condition that had been shown during development and manufacture to infer product performance and is confirmed during the initial process and product validation. This is the direction I think we're going in, and this is where we want to see our processes in the future. Relationships are developed and confirmed with physical and chemical tests subsequent to the

manufacturing runs, and release is conducted by review of process conditions during each batch manufacture.

Some of you are happy to share with us some of the successes you've had moving in this direction. Others of you are excited about making a submission to the agency to get at least part of your system under a PAT system or a PAT method of controlling the process. Some of you are sitting there going, Oh, my God, what am I going to do next?

Well, that probably will continue on for the next few years, but I remind you all that technology has increased at an exponential rate since well before the Industrial Revolution. If you follow the ascent of man technology, every so often there has been a breakthrough and a change. Those breakthroughs have come closer and closer and closer together as we've moved through the last century. If you drag your feet when this technology starts--takes off in the hope of letting it all shake out over the next 10 or 12 years, 12 years from now you'll find yourself all alone and your company significantly disadvantaged.

Product is manufactured according to a

process condition that are responding to direct measurements of in-process product quality where unit dosage forms are being manufactured. Relationships are developed between process and product performance that are optimized and bound by the data obtained in the development and manufacturing runs. Release is conducted by data collection from in-process product or each dosage form during manufacture.

Release specification form validation criteria can be defined for each condition based on the nature of this release, and I think that's where we're headed.

Questions that we think need to be addressed in the guidance as we move forward. Should there be a difference in expectations between the developmental product releases for P1, 2, and 3, then the routine manufacturing lots? And we discussed differences when they happen and when they don't happen.

We kept coming back to the same theme, a theme that I think should be near and dear to everyone's heart in here, if there's good science behind it, and we can explain our decisionmaking based on data that we've acquired and understand;

and if we can understand our process, then we should move forward. And if we can't, then we probably aren't doing the right thing.

Could and should there be official designation for products and processes that are inherently capable of being appropriately measured and controlled would allow for predicting product release characteristics? And I think this is an evolutionary question. As people get more and more understanding of how PAT works, we'll get more and more understanding of how well we can control certain processes and how well they are in terms of predicting the outcome better than we do now.

Content recommendations for the guidance document, suitable for the intended purpose. In other words, the process that you have and the validation you apply should be suitable for the outcome you want to achieve. The general validation criteria, we expect that the agency's guidelines will be in general and not specific. They won't be guidelines that will come out that will tell you how to use a near-infrared to measure content uniformity in a blend, but, rather, that will give you some guidelines in terms of how to proceed.

There will be references to existing guidance documents to help you apply the appropriate document to the appropriate situation. If you have a sensor, you have to validate the sensor. If you have another technique, you have to validate it and so on.

We expect that the agency will allow you to get into the research mode, find out about these sensors before they're applied to the system, without interfering with your attempts to understand PAT in your own hands and your own system. And, of course, there is always the safe harbor which boils down to OOT versus OOS. In other words, if you have something that you see because you have a really good way of looking at it, and it's a little bit out of the trend that ha occurred in the past, that's okay. If it goes out of specs which were previously established, that's not okay. And no matter how you measure something, if you're out of specs, you're out of specs. All right?

So if your old method would have called you out of specs and the new method calls you out of specs, guess what? You're still out of specs.

If the old method wouldn't have noticed

that you're a little off trend and the new method does, you're not out of specs. Your trend has to be watched, and you have to decide as a company how important that trend is. And we can go for exquisite examples, but if you have a 90 to 110 percent active ingredient on your tablet and your tablet is run and you're measuring and you have a system now that tells you that every other run you've had, you've been between 98 and 102, and this run you're between 98 and 103, maybe there's a trend here, but it's certainly not out of specs. You're going to release your product. You're going to continue to march. And perhaps you're going to think about it in terms of internal controls.

Encourage the use of PAT. FDA should encourage it. We see it as a tool to improve the industry's productivity and the quality of the products the industry produces. And so, therefore, the agency as a responsible agency of the United States Government, interested in the welfare of the public, will be involved in encouraging you to use these things to make things better in the long run.

Now, we also looked at a group of questions that were proposed as a result of a discussion between Ajaz and members of the industry

off-line, and we responded to those. And I've chosen not to share them with you one after the other because they essentially reiterate some of the points that we've talked about, and they will be used by Ajaz and the other members of the agency to try to put together this overall guidance document for validation.

So, with that being said, I'm going to stop, and I'm going to turn it over to people in my group who have anything to add. So we have some major contributors to the information we've put forward today, some of them actually hiding in the audience now. And if they have anything they'd like to add or anything they think needs to be clarified, please, do that.

I can't believe that I was that good at summarizing that they don't need clarification. Go ahead.

Don't forget, we need a mike so we can record your clarification.

DR. C. ANDERSON: A very brief clarification on the general validation criteria. One of the themes that came up in the group over and over again is that the accepted validation criteria for method validation are generally

applicable to PAT-type applications, so that line is in there specifically to denote that, that the generally accepted practice for method validation should be continued for PAT applications.

MS. SEKULIC: Just to throw out one additional comment that came out in the discussion over lunch, I guess for the record, if it could possibly be stated so, we keep thinking that we're going to write this guidance and this is it, it's going to be carved in stone. And I just want to throw out there, you know, as technology evolves so does the guidance. And so I just kind of wanted that be recorded, I guess, for posterity.

DR. KIBBE: Like any FDA guidance, they're subject to review and change and update. The FDA has not been carved in stone, even in 1938 when they started actually deciding that drugs might need to be safe to be sold in the United States. So I think that's a really good point.

Anybody else? Does the FDA want to comment?

DR. HUSSAIN: Just sort of a question or a comment on the point you made with respect to the jobs of analytical chemists. I thought with this actually you're going to increase--you have

increased the number of lab-based analytical chemists to do all the calibration work and so forth. So actually they shouldn't worry about losing their job. They should worry about getting an extra burden of more work to do, because I think how--where will the calibrations come from? You have to balance the--so analytical chemists, I think their numbers are going to increase.

DR. KIBBE: Good to know job security is there, too.

DR. SHEK: Just a general question. I would assume--just a point of clarification, there are two aspects of validation. For us it's validation of PAT as an analytical tool, okay? Then validation of the process itself. And I tried to follow up on the slides and whether you are referring--if we are going to use PAT and will basically---let me step back and say validation, the way I understand today, there are some rules. We are saying three batches being tested according to a predetermined protocol and with preset, you know, specifications. And if it passes, we are saying the process has been validated.

Now, if we are going to use PAT, we'll generate continuously, possible, more data than we

do today, not selectively, if still this concept of process validation still exists or now the scheme is a little bit different now, because maybe we are validating every time we make a batch. And I don't know whether that was captured there or not, or that--

MR. FAMULARE: That actually was one of the bullet points in the slide that I thought really hit the nail on the head. The ability exists now with this technology to validate each batch, and that was--the number two bullet point on one of the previous slides.

DR. HUSSAIN: When I saw this, follow the "c", I said it's continuous GMP now.

DR. KIBBE: If you can get the technology set up so that you can continuously follow the process from before the material shows up at your door until the finished product leaves your door, then that's exactly what you have, a continuously--constantly revalidating it, manufacturing process under complete control, that's like the golden fleece, this process.

Now, to think that we're going to have that next week is a little, you know, Polyanna, but to think that that's not an unreasonable goal and

to have the guidance or the guidelines allow that process to evolve I think is what we're hoping for.

MR. HALE: I think there are layers of validation and the terminology is used somewhat loosely. I think that parts of validation will remain similar or not changed at all. The equipment still has to be validated and methods still have to be validated and sensors, too. Probably the biggest change in all of this is this issue of the process and that there was a lot of talk, and I think one of the greatest opportunities in this is to take the larger holistic view of the process and product in mind, and that part of validation will potentially change the most if we can implement some of these technologies.

So I think validation means different things to different people, but the opportunity is in the process and product arena.

DR. KIBBE: Anybody else?

[No response.]

DR. KIBBE: Seeing no one leaping to the microphone, Judy?

DR. BOEHLERT: While I'm waiting for our slides to be mounted, I'd just like to thank all of the participants in our sessions. We had very

interactive sessions from the committee members as well as from a number of the audience members. So my thanks. We were still going strong at 12 o'clock today, so that's a testament to the discussions we had.

Okay. We did take a look at Ajaz's questions and go down them in order because it helped us to sort out our comments. And the first item that we looked at was the R&D focus and what should be documented to justify suitability. And the important thing to consider here is the focus in R&D is different than that is in manufacturing. And R&D is looking at boundaries of processes. They're trying to understand the process. They're not trying to control the process. Manufacturing is more on the lines of controlling the process and use PATs for that purpose.

So during our R&D, the PATs are used to gain understanding. During manufacturing they're used to monitor and control.

Not all PATs will make it to manufacturing, and I think that's an important concept. During R&D you may look at a number of different parameters, and the whole point here is to decide what's important and what's not

important. So it's very common that you'll see that PATs are studied during R&D that don't make their way to the final manufacturing process.

Demonstrate suitability of PAT measurement for intended use. This is a basic principle that I think we need to look at. You know, they're used for predicting very open end-product quality attributes. Some PATs--we looked at three different kinds of PATs that you might use: ones that replace existing technology, if you're doing an assay, you can do it on-line using NIR, perhaps, instead of off-line using HPLC. And that's a replacement, and you can look at equivalency.

There are other PATs, for example, using acoustic technology to get a prediction of what particle size might look at in a granulation. That's a different concept. You might also look at, for example, measuring something like mag stearate as a predictor of dissolution. So each of those is a different kind of PAT that you might look at.

You need to demonstrate that it's validatable. For example, the sensor suitability, location, number of sensors, the number of sensors, as well as traditional measurement attributes that

you might use. And I've got a thing across my screen here. PAT performance requirements--that's interesting. Is there a way for me to move that thing up, the writing here? I have to find the mouse on this one. It's the little button in the middle, right? Unless you expect me to remember what word we had under there. Oh, rigorous. I knew that was--I was trying to think of that word.

But what we're saying here is that PAT requirements are more rigorous if intended use of PATs either individually or as an aggregate combined is to replace end-product testing. There is a difference. If you're using a PAT just to monitor one process or one step in a process, that's different than using a PAT to replace end-product testing. And, therefore, the requirements there would be more rigorous.

Then we looked at--bear with me.

[Laughter.]

DR. BOEHLERT: That's not funny. There are only so many clicks you can do here before it jumps.

DR. KIBBE: This is a process of too many process variables not being under good control, right?

DR. BOEHLERT: Yes, this is not under good control. I have to validate--

DR. KIBBE: I think FDA will close you down.

DR. BOEHLERT: I didn't expect this, but, anyhow, the next thing that we looked at was the suitability of PATs as used in manufacturing. And what we're saying is that the points we stated earlier applying to R&D still apply, but there are some additional things here that you need to consider. And the most important, of course, is your ability to transfer the use of those PATs from an R&D environment to a manufacturing environment. You have equipment design issues, scale-up issues, interface changes, ongoing calibration, maintenance, equipment calibration, consider safety of the operator or final user of that product due to contamination. All of these things need to be taken into consideration because you can't always just transfer that technology from an R&D process on a small scale to a manufacturing process on a large scale.

You may need to look at refining the models that you use. We talked more about a process signature rather than a fingerprint, and we

saw fingerprints as part of that signature, and a fingerprint might be--something like an IR spectrum is a fingerprint, but what we're looking at really are process signatures. And what you need to do in the guidance is define some of these terms, so we're all looking at things the same way. Because in R&D you develop information based on very limited studies, and so these things are likely to change as you move in manufacturing and produce more lots.

The concept of PAT can be submitted as sa protocol in an original NDA or as a prior approval supplement. And then implementation of PAT could be done through less burdensome filing mechanisms, for example, CBE or annual reports. So you would file--you know, what we're saying is, you know, file your protocol for how you're going to bring PAT into the process and implement your protocol. That gets approved, you implement your protocol, and then implementation is through CBE or annual report.

Routine manufacturing using PATs, what should be the regulatory standard for accepting an on-line measurement to replace end-product testing, the level of built-in redundancy. We're saying the

body of PAT information should have equivalent or better informing power than the corresponding conventional approved end-product test. Notice we're not saying it's equivalent, the tests are equivalent; it's just the decision that you make based on PAT has to be equivalent to better than the kinds of decisions you can make now.

We recommend that the guidance include a table, and apparently the CPMP guidance has such a table that shows the comparability of different procedures, PAT and conventional techniques, and that would be very helpful--tablets, for tablets. That would be very helpful to the reader of this guidance.

Parallel PAT testing and conventional testing is going to happen. For in-process and/or release tests, both of them could be subject to PAT changes. Should be performed for a significant number of batches. What we said was probably a minimum of three because that's--nobody does only one, two's probably not enough, and three's sort of a minimum, in the absence of historical manufacturing data, because if you've got a lot of data, you've collected it on other products, then that may reduce the burden if you make the same

change on this new product.

The level of redundancy you build in here is often a business decision. How much risk do you want to take? How much redundancy do you want to build into your systems? So that comes down to each company making that decision.

Identify steps for resolving OOS observations. Under what conditions can end-product testing be used to resolve OOS observations? The advantage of PATs is it may allow selective rejection or partial batch release, and when you use it for that purpose, you may indeed reduce the number of OOS observations you have. So that's good. Within-batch trend information with PAT also facilitates any investigation of an OOS observation.

Until PATs are approved for regulatory purposes, the approved conventional test should supersede PAT results because those are the approved tests. If an OOS result, however, is traced to instrument failure--you know, you've got PAT approved, you have an instrument failure, and you get an OOS result, and you trace it to the fact that the sensor failed, then traditional approved analytical method can be utilized for batch

release.

But once you get PAT approved, that is the standard against which you measure your product. But there may be an exception here. Your sensors all failed, do you, you know, throw out the batch? What we're saying is you can use conventional testing.

I have a page blank here, but using--this question actually addressed method validation. So we deferred any discussion and comment on this issue to the other group, and they've handled that very well.

What criteria should be used to ensure that relevant critical formulation process variables have been identified and appropriate PAT tools selected? Well, the criteria should be based on product performance, adequate process control, and your ability to assure product quality. And what you have to look at are PATS either individually or in aggregate, because very often it's a combination of PATs that gets you to that final product quality control.

What information should be collected to justify use of indirect measurements, e.g. signature correlations that relate to product

quality? Product and process signatures are a sum of multiple measurements, and this is why we don't like the term "fingerprint" because it's all of these multiple measurements you make. You need to demonstrate then a link between the PAT parameter, end-product characteristics. If you're using surrogate kinds of PAT tests, then you need to make sure those are scientifically based. An acceptable variation in the population should be established. So these are all things you're going to need to collect information on.

Finally, where and to what extent should FDA involvement facilitate PAT? Well, definitely we should issue a guidance, define terms, provide a glossary. We've heard that today and yesterday, and we're all looking at these terms in different ways, including things like in-line, on-line, at-line. All of these terms may mean different things to different people so we need to define them. To develop training programs, both internal, which you're already working on, and external, for others in industry and elsewhere that might be interested. To develop workshops and include in those workshops mock submissions, case studies, things that will be helpful to the attendees.

As you already indicated, provide the opportunity for meetings between the agency and applicants that should facilitate these kinds of submissions.

And, finally, to look at global harmonization and ICH guidance as a way to go in the future.

So I would likewise ask if the committee members have anything further to add, but that concludes my remarks.

Not hearing any, thank you.

DR. KIBBE: Thank you, Judy. We have to have an equipment change now. The training team has their own equipment, and they felt--

DR. MORRIS: This will prepare you for the flights home today where you'll probably have equipment changes, too.

DR. HUSSAIN: A question regarding the redundancy, the question you were asking. In many cases, the answer from the working group was often a business decision. But in a sense, if you're looking at the totality of an application and so forth, then should not the level of redundancy be part of that decision, not generally a business decision?

DR. BOEHLERT: Would you repeat that?

DR. HUSSAIN: I think the recommendation from the group was that the built-in redundancy should be a business decision--

DR. BOEHLERT: May often.

DR. HUSSAIN: May often be, okay.

DR. BOEHLERT: May often be, yes.

DR. HUSSAIN: My thoughts were in a sense I think we really need to pay attention to the redundancy if we have to rely on a total systems-based approach for assessing and so forth. And so I was not sure whether it's truly a business decision. It's a science decisions. It's an approval decision in some cases, too.

DR. BOEHLERT: It may very well be. We just didn't get into it in that depth where we said there may be some instances where, you know, it is justified. But, in general, you wouldn't put into place redundant systems unless it provided, you know, some payback to you. You might be willing to lose a batch rather than put in redundant systems.

DR. MORRIS: This will represent some of the products of the training sub-group, working group, and as was alluded to by Ajaz earlier, this is really a key component in getting PAT up and

running in the real sense because it is, after all, the reviewers and investigators who are responsible for making sure that the methods are faithfully--both communicated to the agency as well as making sure they understand the basics of it.

So we started with course objectives as we laid out this morning. We actually did the course objectives in retrospect because we had a good bit of the syllabus in hand, but then went and modified it as well, and the group was very anarchistic. Essentially the committee itself expanded to include the whole audience. There were several reviewers and investigators present as well, which helped us a good deal.

So on completion of this program, the certification program, the participants should be able to evaluate the adequacy and performance of current and emerging PATs. This certification will require a demonstrated understanding of the fundamentals, importance, and impact of PATs, and we have five outcomes, expected outcomes, including the distinguishing characteristics of the PAT. The participant should be able to demonstrate understanding of the distinguishing characteristics of the PAT, the ID and use of PCCPs, because as

Enrico Fermi said, nothing looks as much like a new phenomenon as a mistake. Suitability and validity of statistics, chemometrics, and instrumental approaches to PAT. Typical PAT applications and the associated capabilities and limitations of the methodology, with the understanding that you can't possibly cover all possible implementations. Data handling, analytical control and engineering tools, and vocabulary relevant to PAT.

So these are the outcomes, and I'll go briefly through this, the top line syllabus elements, and then go through a little bit of the course structure, and then, as you like, we can open this to discussion.

We came to the consensus that a background section was necessary. The duration of each of these sections will be the subject of logistical meetings that will follow or strategic meetings that will follow. But the background to include an overview of PAT concepts and examples and a review of pharmaceutical unit operations. This is in recognition of the fact that, in general, reviewers will be typically Ph.D. scientists who are well developed in an area; whereas, investigators will have very broad knowledge, maybe broader than the

reviewers, even, but it will not be as in-depth in some areas. So to try to consolidate this team--which I should have mentioned, which is a real key element; having the reviewers and the investigators together is really what is the heart of this concept, not by our doing but by Ajaz's, I suspect, in that it's really forming a team that is capable of both recognizing the importance of specific PAT issues as well as understanding the implications of their actions when they are reviewing them--reviewing or investigating.

So going on to, again--and this came up in Judy's section. The ones that have stars by them are the ones that were identified by the reviewers and investigators as being elements that should be emphasized. So the PCCP definitions and identification strategies and their impact on sensor selection, this would include a fair amount of discussion of the elements of the unit operations that may or may not lend themselves for monitoring and being able to determine when something is monitored, but not correlated to the final performance evaluations that you are employing.

Measurement systems--and, again, I won't

go through all of these, but obviously the data handling measurement systems and the associated statistics form a large fraction of what needs to be covered to be able to make sure that everybody is familiar with the concepts at the very least.

Measurement systems, which include everything from the description of typical sensors to variations on the techniques that are impacted by the unique features in pharmaceutical materials, then sampling systems and issues, the representativeness, efficacy, timeliness, and the distinction between on-, at-, and in-line measurement.

Data handling--this is Mel's term which sort of served to collect a lot of the activities that fall within a conceptually cohesive element, but from relatively diverse areas, so it has basic statistics, dimensionality, that is the sort of description of it, basic statistics, and then through chemometrics, and as we heard from Art, pattern recognition, process signatures, and fingerprints, including--Sonja just left, but Eva wanted to make sure that we put this in, that the informatics was not an orphan here, but is encompassed in the database design and mining

aspects of the course.

Process control, this was a point of a lot of discussion because there are levels of process control, many of which we don't employ now, but if we're considering the audience that would be in the course and the background they would have to this point, obviously the next leap is that you could do process control so it needs to be introduced. Yet in terms of what will be on their plate most immediately, the areas of batch automation and control implementation were identified as key. So there is a whole range of topics here.

Each of these elements is not going to be equally weighted with respect to time, and the ones that are starred will get more.

Documentation, DQ, IQ, OQ, PQ, and what should be included in each section, and this includes a lot of the details that you saw in Art's summary, which includes through calibration, transfer and maintenance, and data security and audit trails. So these are all topics that were identified as--I'm sorry?

[Inaudible comment off microphone.]

DR. MORRIS: Audit trails, yes. Mike, you'll have to--I was just the secretary at that

point. That's what you want, right? Yes. Yell at him. Not tails.

And then wrap-up and recap. Wrap-up and recap is not just a nice job to see you at lunch. It's really a fairly intensive review of all of the topics, a little more cohesive in the sense of a summary so that we tie typical sensors to typical processes, typical as we say here, basic capabilities, analysis and control concepts, and then case studies to bring this home.

In terms of the logistics, this is just a short list, but it's pretty inclusive. You have to fill in a lot of gaps. There would be a pre-course preparation using materials supplied to the members of the training session, and some materials that they would get on their own, but it would be reviewed prior to the onset so that you didn't spend a lot of time because the duration of this course would be somewhere--the didactic part would be somewhere between one week to two weeks. That would still be titrated. So with the limited amount of time and given the levels of education and experience of most of the reviewers as well as the investigators, it's not necessary to spoon-feed them material they've already had. They know most

of it, some of it better than we do, of course.

The second point--and this is not in chronological order, of course--the evaluation would consist of reviewing of published or generated PAT examples. So, in other words, at the end of the sessions as well as in the homework activities, there would be examples of--excuse me, let me just kill this. There would be examples of processes and--individual processes and maybe whole lines where PAT was employed. And the idea would be to interpret this in a way that would be evaluated by the instructors.

The course structure would be a little different. This is sort of a hybrid structure from some Washington, Purdue, and Tennessee ideas. A didactic portion from, for instance, 8:30 to 3:00 p.m., followed by a team-based case study review. So for the last two hours of the day, instead of lecturing to people who have been blunted and bludgeoned by eight hours of continual speaking, you would go as a group--this would include instructors and students, to go through the case studies together and pull out points and have teams. The initial size of the participants would limit the number of teams, of course, but

eventually.

Then homework would be included, which would essentially be application of the day or the combined days' instruction to sort of build up to the evaluation or the assessment that would terminate the course.

The practical training, which, again, would occur before the final assessment, but the practical training would be divided--this is--a lot of this is open for reorganization, but would flow something like two to three days at Washington, Tennessee, and Purdue, with the individual schools using their facilities and their strengths to broaden the training to the point that people have hands-on experience doing some monitoring, have hands-on experience doing data handling and looking at more than one sensor, so that by the time the participants finished, they've hopefully been exposed to it, at least to the extent to appreciate the problems. And, again, some--one of the reviewers in the audience--I don't see him here, but, you know, he's been looking at applications that had NIR in it. Some of them are 20 years old. So it's not like this is brand new. But to get hands-on I think would be a great benefit.

That's the state at this point, and I'll be glad to try to address comments, and the rest of the team is here as well, if there are any additions.

DR. RUDD: I have a couple of observations. First of all, just to say it looks really good. Where do I sign up?

DR. MORRIS: You'll probably be signed up but as an instructor.

[Laughter.]

DR. MORRIS: Hold that thought.

DR. RUDD: Really, a couple of observations about things that maybe aren't included and, you know, this is in the interest of being constructive.

DR. MORRIS: Actually, if you'll hold that thought for just one second, I'll pull up our "what's missing" list. You can talk.

DR. RUDD: All I was going to say is under the list of process analytical technologies, I don't know whether you've included it with some of the headings you've used, but I'd like to say something about acoustic monitoring, obviously. You've got a phrase in there of chemical imaging, and I wonder if we ought to extend that to include

spectral imaging as well.

DR. MORRIS: Yes, I think that's sort of what we had in mind. It was supposed to be inclusive of that, but maybe we should say it specifically.

DR. RUDD: The other term is--I don't know how common this is, but process tomography. I think there's a whole area there, 3-D imaging of the process.

DR. MORRIS: Yes, there's a fair amount of--

DR. RUDD: You may have included it, so I'm just really--

DR. MORRIS: No, not really, but--

DR. RUDD: Just as a safety net.

The bit that I think is really noticeable by its absence, though, is any reference to the processing equipment itself, so I'm moving away from the analytical. And I'm just thinking, Is there value in an appreciation and an understanding of how the analytical technology needs to interface with the processing equipment?

DR. MORRIS: Yes, I sort of envisioned that as being encompassed in part--and I don't know, Mel, you'll have to correct me if that's what

you're thinking, in the list of going through the unit operations--

DR. RUDD: Okay.

DR. MORRIS: --you would be describing the equipment. Is that--

DR. KOCH: Well, I'm not sure if you're referring to the sample interfaces or just the feedback?

DR. RUDD: Well, I guess what I'm thinking about is, you know, heaven forbid, you could envisage a situation where a perfectly applicable PAT is being used, but maybe the way it's been interfaced with the blender, the granulator, whatever it might be, or even the granulator or blender itself that's being used could be inappropriate. And I think--I would hope that a reviewer would have just some kind of basic understanding of the rights and wrongs of how to do--

DR. KOCH: I think we had one point in there that had to do with applicability--

DR. MORRIS: Is this the one, sensor sample placement and maintenance?

DR. KOCH: No.

DR. RUDD: But I think it's interfacing at

the first level, but then it's about not just have you hooked the PAT and the processing equipment together correctly. It is, is that combination appropriate?

DR. MORRIS: Ah, yes.

DR. RUDD: I'm not sure if I'm making that clear.

DR. HUSSAIN: I think you have--David, for example, a classical example of that is you are doing blend uniformity for a blender and you have a probe in one location, that's an inappropriate--it's not going to catch that spot and so forth.

DR. RUDD: Yes.

DR. HUSSAIN: But it's a tumbling blender, one--so that--

DR. RUDD: It's exactly that sort of thing, just a basic appreciation of the strengths and weaknesses of different processing equipment and how they can be interfaced with what might be perfectly good PATs but used wrongly.

DR. CHIU: Another point is I think for the benefit of the FDA reviewer and investigator, it would be very useful to have hands-on experience in a pharmaceutical manufacturing setting, if some

companies can offer us.

DR. MORRIS: We've talked about that, and Kelsey Cook from Tennessee has talked about that in terms of trying to get into some specific companies with whom they have relationships, and Mel has done the same.

At Purdue, we have a pilot lab set up which would probably suffice, at least for that, but in terms of seeing an operation, there's--in terms of getting in to see an operation, there are certainly potentials that we can view. In terms of hands-on using it, I think that would be restricted. Most of the companies aren't going to want people coming in and actually performing batch production. But, yes, that's certainly on the list.

MR. LEIPER: One of the things that's actually quite interesting, I think the content is superb, but I think the context is--might be a bit that's missing. We've been talking an awful lot about holistic approaches, et cetera, and now we're delving into specific areas, and we could quite easily get into these areas, which are quite--could be quite irrelevant without some methodology to put that in place. And the thing that I see as maybe

being missing here is looking at risk assessment, a formal approach to risk assessment to actually select how you're going to manage your risk, which is what the effective use of PAT is actually about.

Now, FDA happened to have this exceptionally good system, but the industry doesn't know about it. And the other thing that's interesting, and Ajaz made the comment, that, you know, in risk assessment it was for safety and efficacy. But the risk assessment goes back to the design of the process, et cetera. And I feel that if that kind of thing is missing, we could be in danger of what we've been doing in the past, which is to say any problem that we get, the answer is HPLC. The answer is the most appropriate solution that manages the variability and it actually manages the noise in the system, and the way that you do that, I believe, is through good risk assessment and management systems to ensure that that risk that's been identified is properly managed.

DR. MORRIS: Yes. I'm not sure exactly how to capture that, but we'll--

MR. LEIPER: I'm staying for a day.

DR. MORRIS: Okay. We'll put it in as a

formal approach to risk assessment, and maybe we can talk with Mel a little bit afterwards as well.

Rick?

MR. COOLEY: A couple other unit operations that appear to be missing, one was process chromatography. It was--

DR. MORRIS: I thought we had that in there. Did we not, Mel?

DR. KOCH: We don't have it in as a unit operation.

DR. MORRIS: Not as a unit op. We have it in--

DR. KOCH: Analytical technique but not as a unit op. We still have some additions to fill in under measurement systems.

DR. MORRIS: Yes, but we do have in-process sensor--this is where we have it.

MR. COOLEY: Right. But up under your process operations, there wasn't any mention, under separation techniques of process chromatography operations as a manufacturing step.

DR. MORRIS: As a manufacturing step. Yes, I think we were sort of lumping everything, including distillization--

DR. KOCH: That's a good point.

DR. MORRIS: Crystallization.

DR. KOCH: You could add chromatography under--in addition to separation, or in addition to extraction.

MR. COOLEY: Also, I don't know if you would like to have filling operations on that list of unit operations.

DR. RUDD: I think actually there's quite a few missing, you know, things like compression and suspension preparation, that kind of thing. The list is not comprehensive.

DR. MORRIS: Right, right.

Let's see. Who's not here? Eva. Send all of your suggestions to Eva.

[Laughter.]

MR. COOLEY: Was there a mention in there on validation, like software validation and the analyzer validation?

DR. MORRIS: Yes. Well, there's a couple of places. In the DQ, IQ, OQ, PQ, there's--

MR. COOLEY: Okay, analyzer--

DR. MORRIS: --analyzer validation.

MR. COOLEY: I don't know if you need to spell out software validation since that's going to be an important part of it.

DR. MORRIS: Yes, I think that's--that was somewhere. I don't know what happened to it. Was it specific somewhere? I can't remember.

DR. KOCH: We thought the vendors mentioned yesterday that they had that taken care of.

MR. COOLEY: Okay. Could I get his name?

[Laughter.]

MR. COOLEY: Then one last thing. It's kind of like David was talking about, ensuring that what the analyzer is seeing is correct, and that could be as simple as how do you know that a window isn't blinded or a sensor's window isn't blinded during operation. Have you taken that into account to assure that that doesn't occur? And if it does, how do you detect that? And extending that further into an on-line analyzer versus an in-line analyzer, if you're extracting a sample from the process, you know, review with the person to make sure they have something in place to ensure that they're getting the valid sample to that analyzer.

DR. MORRIS: Yes, I think we have a separate sampling section. I can't find it right now, but it's in here somewhere. Here we go. So in here you're saying--

MR. COOLEY: Maybe cover it by just mentioning representative. That may take care of it.

DR. MORRIS: Right. I mean, these will have to be fleshed out a good bit for the actual didactic part. And, hopefully, I mean, if you come and watch a line where you're doing a wet granulation on-line, you'll have to become sensitive to a window filing and things like that as your data flat-lines.

[Inaudible comment off microphone.]

DR. MORRIS: Yes, right. You can get a--you can really come to an endpoint quickly.

MR. HALE: Ken, did I see this was a one-day course?

DR. MORRIS: Oh, no, no.

[Laughter.]

DR. MORRIS: Half-day, half-day. Just 8:30 to 3:00, that's it.

No, no. It's somewhere between a one-week and a two-week didactic. Then the two- to three-day stints at the universities or companies would follow that. I don't know if they would follow right on top of it. It would depend.

DR. HUSSAIN: And which school will give

the master's of science in PAT on this?

[Laughter.]

DR. MORRIS: I don't know. Maybe Wilkes.

Anything else?

DR. RAJU: I thought it was a really nice course formulation. I can't believe you did this in three hours.

DR. MORRIS: Well, actually a lot of this came--was done--Ajaz had given us--if you remember, Kelsey, Steve, and Mel all submitted some, so we had a good backbone to start with.

DR. RAJU: It was interesting to see that you had performance evaluation at the end to figure out if the people you were teaching were taught well and learned well. And I notice that you used a case study format to do that evaluation.

First, why did you choose that? Why did you choose not to include more of a theoretical understanding as a second measure of testing? And, third, how do you make that case as real as possible to the industry situation they will ultimately review?

DR. MORRIS: Let me just preface it--wait one second, Mel, let me just preface it by saying the homework is actually an ongoing evaluation

process.

Go ahead, Mel.

DR. KOCH: The purpose of putting the case studies in there is that we were going to try to make sure that we reflected back on the case studies as ways to have demonstrated some of the theoretical things.

DR. RAJU: You would connect them back--

DR. MORRIS: Yes, we would definitely link them back to the theoretical--the physics and the engineering essentially, but in a context that they would typically find themselves working in. But the homework would be the ongoing evaluation.

DR. WORKMAN: I keep looking at that and I see chemometrics, and yet many of those topics are chemometrics. So I was wondering how you are distinguishing that item from, say, correlation, pattern recognition, other things that are normally grouped in that category?

DR. MORRIS: I'll have to defer to the University of Washington for this.

DR. KOCH: We still have to refine that, but it started out as a list of all those things that when we're leading up to chemometrics and actually we stuck in the basic statistics as a way

to get the ball rolling. And certainly we can refine because you get into regression and some of the other things, and, yes, they could be subsets of--this is still awful early in terms of finalizing it. We weren't sure there was a chemometrician left in the crowd.

DR. MORRIS: Is there something that looks like it ought to be altered?

DR. WORKMAN: Well, I would suggest you take out chemometrics and put, you know, other items specifically that you will cover that do fall within chemometrics, or put everything under chemometrics that refers to chemometrics. Either way.

DR. MORRIS: I think there will be, as Mel said, there will be a list under chemometrics by the time the participants have to weather this.

DR. RUDD: There was a point coming out of our group which Judy included in the summary that I'd really like just to bring to the fore, and that is that we see a program like this as being applicable to R&D people from industry as well. This is not just about educating the reviewers.

And I think, you know, speaking personally, I would say the creation and existence

of this program really is an important step and a strong message to, I guess, address the issue that Ajaz talked about in the first session yesterday, which is that one of the barriers or one area of resistance, passive it may be, is actually within R&D in the industry, and we need things like this, an accumulation of things like this, to really bring that message out and to create the incentives that R&D needs to do all of the exotic but additional stuff that we've been talking about in the last two days. It's important that it's good. It's important that it exists.

DR. KOCH: To add on to that, I think that's definitely a situation that needed to be addressed with regard to R&D. But I think there's another group that's intermediary between these, and that's the regulatory affairs and quality assurance groups within industry that are going to be reluctant to move things through unless they understand some of the basic terminology. So there may be a remedial course of some kind.

DR. MORRIS: But I think there's also--there's a clear intent that the course transition to a broader audience, is my understanding.

DR. KIBBE: Has anybody discussed the possibility of either putting this on-line or taping it and then getting a bigger distribution?

DR. KOCH: We're trying to at least get it on paper here first.

DR. MORRIS: But it's a good idea, particularly for people who can't make it.

Anything else?

[No response.]

DR. KIBBE: Thank you, Ken.

We're moving along at a breakneck pace. This is the kind of efficiencies you get when you put PAT in your process. You get to end several hours early and brave the weather.

I believe on my schedule, this is where Ajaz gets to do his two-and-a-half-hour presentation in 20 minutes.

DR. HUSSAIN: Well, I think this second meeting is coming to an end. In many ways, I think my emotional highs and lows sort of reflect the first meeting, again. I was going down, down, down the first day in terms of, you know, what to expect from this meeting, and then it sort of comes back again and gives me much, much more hope to move on. And I think this meeting again did that in the

sense that the types of recommendations and information that you are providing is very, very useful to us and it keeps us going and making sure that we're on the right track.

So I have some sort of closing remarks and sort of next steps here, and I thought I'd start with a reminder. One thing that sort of started pulling me down the first day was the discussion on flaws, flaws, flaws. And I think a reminder to myself and to everybody is that we--I personally believe the quality of products available to U.S. patients is good. In fact, I think when we go to India every other year on a long trip, we take all of our medicines from here. And my wife is a physician. She won't buy anything from there. So you can see how much faith and trust we have.

So just personally speaking, as a consumer, and also from an FDA perspective, I think the PAT initiative did not raise that as a concern. And I just want to remind us that we are not questioning the quality of products available to the U.S. patient. It is good.

Why is it good? And I think the current quality assurance system, which is setting the specifications, cGMPs, and the testing, is able to

prevent the release of low-quality products. I can just look at the number of Class I recalls. They're very, very few. You can count on one hand the number of Class I recalls.

There are a number of Class III recalls which I think to my thinking reflect some of the efficiency issues that we are trying to talk about. But from a safety and efficacy perspective and the concern, I don't think we have that concern.

So what we are talking about is that currently level of process understanding is low and, therefore, requires a very high level of scrutiny and need to reject product of unacceptable quality.

I believe the reason for that is our process understanding has been limited because we deal with complex systems. These are not simple systems, although a tablet looks simple, but in terms of physics and chemistry, it's quite a complex system. It's multivariate, and traditionally we have approached formulation development as--I used the term "odd" (?), and I'll use it again, with the perspective of saying that--I mean, that's how we emerged in terms of developing formulations and so forth. And the

tradition has been, as we treat these systems as univariate systems, and we do one factor at a time experiments and somewhat trial and error experiments. So it really doesn't give us the level of information that I think is now needed. It was okay 30 years ago, but now I think we are dealing with far more potent drugs, far more complex drugs in terms of their physical and chemical behavior.

I think we have reached a limit of what our empirical approaches have been able to provide for us in the past. And when I talk or when Janet talks about empirical-based GMP, it's not--it's sort of a criticism of the GMP, but it's essentially a criticism of the data on which the GMPs are based. The data itself is empirical trial and error, so what do we expect?

The other aspect, I think, I strongly believe that our raw materials, especially excipients, are not well characterized. I don't see a solution to that in terms of functionality test as a solution to address that issue. It will help, but not truly. PAT I think brings the issue more directly on to the mixture that we're interested in.

Our equipment selections have been by tradition, and the process factors that we deal with, we generally have limited information. And the question, at least from the FDA perspective, always seems to be: Are they truly optimal or not?

We have development crunch, and clearly, post-approval changes that require prior approval supplement is a hindrance in the process. So combine all this together, I think we need--or we have a system which can really be improved. And efficiency, although not directly linked to quality, I think there is a link. Because if you have low efficiency, you actually have a risk of poor quality. I'm not saying we have a risk of poor quality. If you have enough resources and so forth, the quality is maintained. But our resources are getting tight and tight. So I think we are working harder and harder, and there comes a point when the system starts breaking down. And before that happens, I think we need to change. And so we have an opportunity to change and improve before we run into a crisis.

So, again, limited but sufficient for approval process understanding can lead to it, because that's the current situation. Low process

capability, scrap, rework, recalls, protracted production cycle times and low capacity utilization, resolution of process-related problems slow and difficult, and high cost of compliance.

But from a public health perspective, it leads to risk of drug shortages, and we deal with that on a daily basis. Releasing of poor quality product, recalls, here I would put the Class III recalls. Delaying approval of new drugs, again, at least since I joined the agency, the last three, four years, this is when we are seeing quality problems holding back your blockbuster drugs.

Quality problems also we've seen can confound your very expensive safety and efficacy database itself. And keep in mind, quality is the foundation that allows you to make the safety and efficacy decisions that you make. The other way around, if you say it's safe and efficacious, you can't change the quality standard. So I think that has to be sort of understood.

So the next step, I think, what are the approaches available to us? Approach 1, Option 1, increase the level of FDA scrutiny. However, FDA resources are limited. While the numbers of product and manufacturing establishments are

increasing, our number of folks available for inspection are the same or are going down. And our ability to inspect, our ability to manage the review and assessment process is being challenged in terms of the resources that are available to do that.

So we felt Option 2 was a better option: increase the level of process understanding so that allows us to prevent rather than scrutinize much more. And PAT is being used as a model system that's not only technology. There are other approaches to this. But PAT is a way for us to move forward and hopefully bring other technologies and other approaches along with it.

So the current system in a sense is predicated--it is very essential to have very strict adherence to SOPs and all other documented procedures. This is a critical step in the quality assurance. So the cGMP part, without the cGMP part, the testing literally will not have any value. So the two combined make sense for the quality system. So the GMP part and the testing part are both part of the same system, and each is an extremely important step.

We have re-specified time and testing, and

we use that to document conformance. We have univariate assessment not a systems approach for quality decisions. Learning essentially stops after validation, inability to connect the dots, and the system is not conducive to continuous improvement.

We are hoping that PAT system will address some of these things. Why? We hope to have more performance-based assessment, and we can use this to conformance throughout the process and prevent manufacture of unacceptable end-product quality--or prevent manufacture of product--of unacceptable end-product--I'm saying (?) . Systems approach for quality decisions. Why do I say systems approach? I think when you start looking at process and you're supposed to make decisions of releasing a product on the basis of process data, you have no choice but to look at a systems approach. You have to look at every part of the system and connect every part of the system to make those decisions correctly.

Learning and validation is continuous. We can--some of the dots that we are missing are connected, and this continues there. I hope this will be a process which is conducive to continuous

improvement. It will be a challenge, but how we set that, I think we have to make sure our first guidance is in that--is moving us in that direction.

Clearly, we'll still have strict adherence to SOPs and all of the documented procedures. But how we arrive at these SOPs and how we arrive at the documented requirement will now be different because of the higher level of scientific understanding and so forth. So you're turning things upside down in one sense. Hopefully that will be the right approach, and I'm hoping that with your help we can make sure it's the right approach.

So there are seven emerging PAT guiding principles. Too many spelling mistake. I didn't check my--anyway, let's look at an NDA or an ANDA situation. The guiding principle here is whatever we do, we should not prolong the review times due to introduction of PAT. How we do that, early meetings with PAT reviewers, industry meetings with PAT reviewers. Expert technical support available to these reviewers, and we are creating a group of four or five individuals with expertise in PAT available to serve as consultants to our reviewers

and inspectors.

At these early meetings, we will identify GMP issues and discuss it with the PAT inspector, possibly have reviewers participate in pre-approval inspection with the PAT inspection, so you have a team concept. And also consider interim specifications for PATs. Clearly, we know that you will need far more data. The three batches for validation, the concept, may not be suitable for PAT, but it doesn't mean that you hold back your approval. You'll still go through the same procedure, but you would finalize your specification on PAT later on as part of the Phase 4 commitment.

In the post-approval world, at least in my mind, the scenario is a company will go out and collect data to establish PAT proof of concept or suitability. We may or we may not be involved with this process. This could be a totally independent process that a company does on its own. But I think if a company wishes to talk to us, at this point we could consider making ourselves available to see whether you would agree with the processes that are already started. But that's an option.

Then once a company has collected

information to establish proof of concept and suitability, we could have a PAT meeting. It would be sort of a special meeting to come and talk about how a company wishes to bring this on line. And actually we're going through one--we actually went through one such meeting in May with the first company that has come through with a PAT submission.

So a PAT meeting with the PAT team. The goals and objectives of this meeting would be to develop consensus on how to introduce PAT on an existing line and questions to be addressed or data to be collected for validation. Discuss the safe harbor concept. What would that mean to that particular product? And then work out a submission and inspection strategy--when, how, what should be done?

Continuing on that, I think FDA will focus on a high level of training, communications and a systems approach to review and inspection, and here is the CDER/ORA team approach. My hope is that we'll have minimal reliance on the prior approval supplement process. We haven't worked this out, but we will keep this in mind as we move forward, find ways to have minimal prior approval type of

requirements for PAT, because you already have an approved system, so we can actually think of moving towards annual reports and other types of mechanisms to do this. That probably decreases certainty much more.

Increased emphasis on underlying science and mechanism and assess risk of poor quality. In our discussions and our meetings with the companies, these would be sort of more emphasized than what we do today. I don't say that we don't do these things today, but I think this becomes a much, much more emphasized aspect.

Now, the question is: Is industry willing to move on--I can't speak for the whole industry, but at least one or two companies which have already indicated they're moving in this direction, one has met, the other company we hope will come and meet with us soon. So, clearly, FDA is not the hurdle. So three years from now if this doesn't happen, don't come to FDA and say you were the hurdle. I think this is over. You don't have this excuse anymore.

FDA is working with industry to minimize the risk side of the equation. Industry has to determine the benefit side of the equation by

itself. I don't think we can help--although there was one suggestion that FDA should define the benefits. I don't think that's our role.

Success of this initiative depends on one or two companies who will take the lead. So far, I think we're very fortunate we have found those companies. Hopefully this process works out with those two.

Can we afford to fail or not move forward? I think you have to make that decision.

Sort of wrapping up, one thing which sort of pulled me down and I was feeling a bit down for this meeting was--I said we didn't plan this meeting well. We had time left. We could have done more. But, anyway, I think Meeting 3 had very different objectives in mind. The discussions on general principles of validating computer systems and models, especially Part 11 issues, whatever that needs to be discussed, we will discuss those there.

We'll have a dry-run exercise on a mock PAT application, review and inspection decisions. Need case studies. We set up two mechanisms to get case studies. The docket that was talked about--you have the information in your packet--was

essentially created to get these case studies. And what I would like to do is members on this committee sort of contact different industry members and see how we can get examples and create these case studies, and we can structure the meeting or a working group session at the next meeting so that we can actually--since we have already identified the reviewers and inspectors for PAT, we can have them go through the submission, although they would not have gone through the training, but at least we can see whether we can do a mock run. And that would be, I think, an important aspect of the next meeting.

We also wish to discuss issues related to rapid microbial testing. What information should be incorporated in the general guidance to address rapid microbial testing? One of the major concerns expressed by microbiologists was that the chemistry part cannot handle the microbiological part. There are significant differences. But the general guidance is not specific to any technology and so forth. The general concept and principles should essentially be sufficient here, too. But we would invite some of the microbiology experts to come and talk to us next time, and we will go through this

discussion and make sure the general guidance can have one or two paragraphs to address these issues also.

What I plan to do is have this group essentially run in parallel. When we have the microbial discussion happening in one room, this group could actually focus more on the dry-run exercise. So we can have those two happen in parallel so that we can do a more efficient job of completing the program in one day.

NIST has expressed an interest to hold a workshop at the time of the third meeting, so there will be an optional workshop at NIST. I don't have the program defined or anything, but if there is interest, we would work towards a workshop where NIST would like to sort of share with the group development of reference standards, development of calibration standards, even computer validation aspects, what they have been doing. So there is a possibility--I can't promise whether this will happen, but we're working towards an optional workshop for people to attend this the next day or a day before, whenever this meeting is.

So that's the next step right now. I'll stop, and if you have any questions, I'll be glad

to answer them.

DR. KIBBE: Anybody? Anybody determined to have the last word? Yes, sir?

DR. RUDD: I'll go for it, Art. I'm sure it won't be the last word, but I'll go for the second to the last word, maybe.

Just a point of protocol. How quickly can we get copies of those summary slides? I'm thinking for internal purposes they would be extremely useful.

MS. REEDY: These will be on the Web probably Tuesday.

DR. RUDD: Okay. That's good. Thanks.

And really just a question, Ajaz, about the rapid micro. I just wonder if we could gain any prior experience from the food industry, for example. I'm assuming they must have addressed that issue before us.

DR. HUSSAIN: I think since I have not been involved, I'm going to have the micro folks handle that part of the discussion. So I don't have that expertise.

DR. KIBBE: Anybody else have any questions or comments? There's someone behind you, Ajaz.

MR. RITCHIE: Yes, a question in terms of the availability of making your PAT--not a road show, but if I needed to do more than I'm doing for my company, would it be possible to hear from you live at my site?

DR. HUSSAIN: Well, I've been on the road show for a long time now. Definitely I think we would love to come and talk. In fact, on Monday I'm driving up early morning to Teva Pharmaceuticals. So I'll be spending a day with Teva Pharmaceuticals in Pennsylvania. So, Gary, send me an invitation. We'll have either me or somebody else come and talk to you.

DR. KIBBE: Okay. We're coming to the end of our two days of discussion. I want to thank all of you for your contributions, your patience with some of my poor humor, and I'm sure that what we've done will have a lasting effect on the industry and the regulatory body and the public that we serve.

Again, thank you. Have a pleasant trip home, and we'll see you at the next meeting.

[Whereupon, at 2:38 p.m., the meeting was adjourned.]

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