discussion which we may be on a different page with Europe--the European agency, with respect to parametric release, so this would help us, in a sense, formulate our thoughts on, is parametric release very different from the CQV or whatever that concept is?

DR. LAYLOFF: I think the--and, certainly, in the United States, it would be very different, because in the parametric release, the product itself that's being released has never had a measurement made. So it's a really a leap of faith based on your measurements on a surrogate that allows you to go forward and this is not anywhere near that.

DR. RUDD: Yeah, if I could just comment on the European situation. It's fairly timely because Ajaz referred earlier to the CGMP EMEA guidance on parametric release, which appeared, I think, during the end of last year.

There has been a small working party commissioned by CPMP charged with the task of providing more extended guidance. So it's industry providing some input now to CPMP to maybe to close the gap a little bit. And a number of us, potentially from AstraZeneca, Pfizer and

GlaxoSmithKline, in the U.K., have recently developed some guidance which has actually been presented to CPMP today. I think it was inappropriate to circulate that draft document to this group before CPMP saw it, but I'm more then happy to try and do that immediately afterwards.

It is narrowing the gap. It does reflect very much the quality-by-design concept. The parametric release term, which I think has been a bit of an albatross for a number of years, because it is historical and does mean a number of different things to different people. The proposal is that that's being replaced with the term real-time release and the document very much develops the quality-by-design concepts. And I think it does--it does close the gap, as I said, between the position I think this committee's at.

But it does also provide an extra piece of information which I think could be very useful to consider here and that is some proposals which clarify the relationship that could exist between a process-based measurement and the end product quality attribute, that might be predicted by that process measurement. So, to give an example, I mean, despite what PQRI might tell us, I believe

intrinsically that there's a relationship between powder-blend uniformity and tablet-content uniformity. It just seems intuitively right to me. So that's a nice one.

Similarly, you can make a relationship between powder-blend assay and finished-product assay. And the document attempts to derive other relationships. So, you know, what combination of measurements could you make which might be predictive of dissolution testing, for example. I think that's a very useful point and I think any guidance that we eventually develop would be well advised to try and address that same point. Maybe not in the same way, but not to leave that point untouched. I think the gap's closing, that's the import thing.

DR. HUSSAIN: The historical sort of baggage with the term parametric release, I think I'm very pleased to hear that at least they're moving away from that because parametric release, I think, Tom, in your presentation--in the recent meeting that we were together--in essence, creates a scenario where I think confidence is not there. So even when you have parametric release for parentals, people just do the test anyway for the

fear of lethal concentrations and so forth.

So moving towards more science-based measurements, I think, sort of alleviates some of those concerns associated with parametric so.

DR. LAYLOFF: I think in our earlier discussions, too, there's no intent to abandon all testing and stability testing would be there and things like that. It's a different ball game. I think Questions 2c, I don't think we need to address. Going on to Question 3: Does the Subcommittee wish to refine or modify the working definition f PAT proposed at its first meeting in February? If so, how should this be modified?

DR. HUSSAIN: The definition that came out of the--by the benefits working group, was, essentially systems for analysis and control of manufacturing processes based on timely measurement during processing of critical quality parameters and performance attributes of raw and in-process materials and processes to ensure acceptable end-product quality at the completion of the process. That was the proposed definition by the group and I think, keeping some of the thoughts in mind what David sort of summarized them so that different aspects of PAT in different arenas of

development and so forth. Would we want to stay with some similar definition or sort of modify this?

DR. KOCH: Yeah, I think this fits very well. I think the emphasized word there in the definition is going to beg for some dynamic, timely definitions of critical. And I don't thin it needs to be in the primary definition, but I think there'll be a subset of what is critical at this time, based on technology or performance.

DR. MARK: I think there's a word coming in here which we first heard from our European friend and I'm hearing it several times. And the keyword here seems to be time. You can imagine a whole range of possible technologies in use. Some will give an answer in a second, some in a minute, some in an hour, some in four hours or whatever. And the question then becomes, well, what do we mean when we say timely? What do we mean when we say real-time? I think this is a question which sooner or later is going to have to be addressed.

DR. SHABUSHNIG: But, just to comment back--can't that be left in terms of the context of the process that's being measured? In other words, if you have a process that's a two-day process, an

hour measurement periodicity may be appropriate, whereas, if you have a process that takes a minute, you need something tighter. And I'm not certain that we want to constrain ourselves in the definition at this point. I think there has to be appropriate science around what the appropriate timeliness or measurement interval should be.

DR. MARK: That may well be--that it will have to be, as Ajaz said, every new technology will have to have its own SOPs, but I think sooner or later that is going to have to be something that's going to have to be part of the definition.

DR MORRIS: Just to Mel's point, if I can for a second--oh, sorry, did I step--very briefly to critical--the word critical here. It may not be necessary, only in the sense that you may be monitoring parameters that, independently, don't constitute a critical component, but when taken in conjunction with others, give a signature as, David I think you had mentioned last time, said would be the real metric.

DR. RUDD: Yeah, if I could just come back to that point about the real time concept. And I think John's comments are exactly right. It is, obviously, process-dependent.

As an example, I think all we're really talking about with this idea of real time is the ability to--and this is very much in the manufacturing environment--is the ability to make a measurement and then do something about it, in terms of corrective action, if that's what the process needs. So it's a time frame whereby we're not just making a measurement, it's a measurement that we can react to. One example I got from the food industry in the U.K. And this is particularly important for continuous processing, a lot of their analysis is very much off-line, still laboratory-based, but with extremely rapid turnaround of measurements so that they can actually go back and correct the process or take a time slice out of the production material, if the percent was out of control, particularly. So, it's just--just really that. It's about making a measurement that you can then do something with, you can react to--feedback corrective, action, rather than just make a measurement and write it down and never do anything with it.

MR. COOLEY: One comment, David, though is, when you say it's a measurement that you react to, you know, are we limiting the application of

PAT by saying that you have to react to it or you have to control something with it because, as you mentioned earlier, going back into the process into development is where there may be great benefit of PAT that the subcommittee's not really addressing.

And in that aspect, it may be just monitoring what's going on and doing no control whatsoever. So I would challenge that maybe we need to take the word control out of the definition and make it a timely measurement that lets you understand your process.

DR. RUDDER: Yeah, I mean, I did preface it by saying, in the manufacturing environment. So, yeah, simply making the assumption there, that if there is a need to make the measurement during manufacturing. And don't forget, we might well do enough in development to establish that we don't actually need to measure anything on a routine basis. But making the assumption that if we are making a critical measurement, during manufacturing, then, presumably, you want to do something about it, if the data from that measurement is not what you'd expect, hence the reactive component.

But, yeah, you're right, I prefaced it by

saying in the manufacturing arena. And that's the only scenario where I think you would need to use the measurement in a reactive sense.

DR. MILLER: And that goes to what we have discussed in the past, in the previous meetings. I would like to add, for clarity of thought, I believe, two sentences are better than one long sentence. It aids in thinking and appreciating the concepts. And let me, suggest a little refinement to the point of the beginning of the first sentence and the beginning of the second sentence. I would like to see something in this order: Systems for analyzing and controlling manufacturing and delete of. This first sentence ends with the word processes. The second sentence begins with PATs--capital-P, capital-A, capital-T, small-s assure acceptable end-product quality at the completion of a pharmaceutical manufacturing process. This two sentences to me, aid in clarity and allow for, let's say bigger thinking. It separates and allows for thinking. My small suggestion, thank you.

DR. HUSSAIN: One sort of aspect, which David raised was that in development we may find, using all the technologies that some things need

not be measured. So the definition in the development arena and the manufacturing arena could be slightly different. But, essentially the technology which I would also sort of ask you to consider is, would design--statistical design of experiments be part of PAT? And this was a discussion we had at the first meeting, because now, instead of doing a trial-and-error type single-factor experiment, we developed a product and we have very little information about interactions and so forth.

But now if a company opts to do a well-designed experiment, some companies do that now--and would that be considered as PAT, because one of the suggestions which I didn't put as a question was to change the name to Process Assessment Technology rather than Process Analytical Technology. My personal feeling, analytical is assessment so that--that goes to that point in the sense--would something have to be measured to be PAT? Is that question, so.

Dr. CIURCZAK: I had a thought about what Rick was saying. We're moving to a conclusion here in terms of controlling and looking at every--eventually looking at every tablet, some

people would like. And we forgot some of the early work that Ajaz brought in. Some of the people who spoke of this taking a year or so, sometimes to make a process because there's large gaps. And should PAT encourage just substituting things, like, sticking in a probe to measure moisture rather than sending it out for Carl Fisher, et cetera, et cetera. In other words, shorten the process as it now stands. Give some feeling of confidence to the process engineers that these probes give us good information and work so that they'll eventually buy into the tablet-by-tablet down the line.

I think in terms of, if we waited for the Mustang--Henry Ford had waited for the Mustang, we would have been riding horses from the early 1900s to 1965. If we want to encourage instrument manufacturers to progress to the point where we have the speed, accuracy, precision to read tablets as they come off the press in milliseconds. If in the meantime we allowed them to make a living selling their instruments for such things as putting a probe into a granulator or a blender or things like this, you jump--you can't go from a grandfather clock to a quartz watch in one week.

And I'm thinking that if we focus totally on total control, are we now taking away from the very large and very real economic benefits of putting process, on-line instrumentation into play where we now take samples up to the lab and cut something from six months to six weeks. And wouldn't that, indeed, give everybody involved, including management the confidence to say, hey, they were right there, they're probably right about this PAT think now and let's control everything.

DR. BOEHLERT: I also would suggest that, perhaps, we can clarify this definition by dividing it up into two sentences. Right now, the way I read it is the focus is on the process with the dosage form and controlling and monitoring that. And, in fact, if you haven't controlled and understood the properties of the excipients and active ingredient that you put into that process, there's no amount of controlling and monitoring on the dosage form process that's going to give you a final product. It meets all requirements. And somewhere we need to get that thought in there.

It now talks about performance attributes of raw and in-process materials, but that's not something you do during the processing of the

dosage form, that comes before, hopefully, you don't want to--not always, but hopefully, you don't want to start and find out you've got a problem midway through the process.

So you might want--if you divide that into two sentences, you might be able to get that thought incorporated.

DR. MORRIS: Yeah, and just to follow up a bit on your point. I think is that, certainly, the intent is not to exclude individual monitoring--monitoring of individual unit operations or certainly not API or excipients. Is that served by broadening this to not just--to be not just inclusive of manufacturing processes but to break it down more in the language to ingredients, unit operations and processes? I mean, it could be that simple.

DR. SHEK: I think, it's there. It talks about raw materials, right? The way it's written now, it says, that--

DR. MORRIS: Right, attributes of raw--

DR. SHEK: --attributes of raw materials. So I thought that's what, basically--

DR. MORRIS: Yeah, I was just saying to change the language to be a little more specific to

say, you know, pharmaceutical unit operations and actors and excipients, but that might address--well, I mean, just so it doesn't exclude that.

DR. ANDERSON: I'd like to ask a question. Are we talking about a method of providing information and the quality of whatever it is we are manufacturing at various stages of the game, so to speak. And what we do with that information depends on what the information says. And if, in fact, my understand of this is correct, then it's not clear to me why control is a part of the definition. So, my question is, are we looking at a method of determining the quality of whatever it is we're doing at a given stage of the game, as opposed to actually having a system that controls what happens when we find something? You understand my question?

DR. KIBBE: All right I have that--the burden of authorship, I guess. This definition was the result of a lot of discussions about what we think process assessment technology or process analytical technology can do for the American public, for the agency, and for the industry. And we think it can do a lot of things beneficial for

all of us.

First, it can, in some places replace older methods of releasing batches, more efficiently, more actively and more in a better way. In some places if applied correctly, it will help the company even control their own process so that they don't have to worry about the loss of a batch because the process starts to go bad part way through, they can monitor it on an ongoing basis, which we put in as timely, and make adjustments.

It improves the process because it will allow release quicker and, therefore, the timeliness of the information and the release of the batches and the time it takes to do a batch or do an individual product gets shortened and the cost to the company gets better. And it makes it, in some ways, easier for the agency, because the agency can then depend on a whole set of ongoing information whenever it reviews what's going on and it doesn't have to look at snapshots.

And we've recognized--and I hope most of you understand--that some of the snapshots that we use now to release batches are not very statistical powerful. We take very small numbers of tablets to decide that we're going to let a million tablets

walk out the door. And we are going to feel, I think, much better about all those decisions when we put things like this in place.

And hence the agency, and I'm going to speak for the agency, even though I'm not in it, is very encouraging to get industry to do this because it then increases their level of confidence that good decisions are being made on a day-to-day basis that affects the health and well being of the American public.

So, yes, control is important and it's part of it and we're not making purely a regulatory definition, we're making a definition, everybody can work with and use in-house or on a regulatory basis and so on. And so I think that's important.

Timely is important, because information that's untimely is what we do now. So, I mean, we're trying to get better at this process. And so, I think some of those terms are good, now.

I agree with my colleague over here says that if you have a sentence that goes for more than four lines on a typewritten page, it probably is going to be confused. And the people who will confuse it the best are the lawyers. And I apologize to all of you out there who might be a

lawyer. But they will, you know, just--and I think we might want to strengthen the definition on a regulatory side of the aisle by breaking it up into bullet points or something where we know clearly, exactly what we want.

And I also know that wordsmithing using 28 people to do it is a nonproductive process, okay? And while all of your suggestions are great, I think it's probably a good idea to let one or two people sit down and try to come up with the next stage of it. So, I hope I've helped.

DR. ANDERSON: Let me just clarify. I am not against the word control, what I'm--if you're talking about an NIR system, the NIR system doesn't control anything. It provides information. I think what I'm questioning is the placement of controls and in the sense--control in this particular sentence. It's not the system that does the controlling, something else happens as a result of the information that's provided by the system.

DR. HUSSAIN: To clarify, I think when we talk about PAT, we PAT because we said measurement information technology, the feedback control--the entire thing is a system in our mind. The measurement part is just one part of the system.

DR. MILLER: It goes back to the English. The system is analyzing and controlling, which is different--that what I want--I want gerunds in there, it's too passive and it goes to subject for confusion and other interpretations, so I agree, I agree a couple people need to wordsmith it and get it into a couple of sentences or bullets and that's how we'll work our way out of it.

It's--the more you think about the way it's written, it allows for too many interpretations.

DR. LAYLOFF: Okay, I'm going to invoke the Kibbe rule and we're going to stop discussion and Ron, you can talk to Ajaz.

MR. CHISHOLM: Yeah, can--I mean, just as an example. I was fortunate enough that we had our senior management together dealing with us and Ajaz last week and I put the definition in front of them, thinking it would all be wordsmithed and changed, just you all are doing at the moment. And lo-and-behold, not one single word was changed. All they said was, let's hope that the people that David was referring to--the definition that comes out of Europe and that lot and the definition that we have here are harmonized in some way, because I

think that's probably quite important from an industry viewpoint.

I'd just like to guard against one point. We, as an industry, do not intend to test every tablet under any circumstances, because there's statistically no need. It would be going from the sublime at the moment to the ridiculous. We will test a significant sample, which I think is where we need to be.

The answer to your question, I think, Ajaz actually answered and that is that you have to think of these systems in their entirety. We would, in fact, gather data in batches, that's on the raw materials, blend times changing, the tablet analysis, et cetera. Over a large number of batches. Firstly, we'd do it during a batch to make sure we weren't going out of specification. But our data would then be, as it were, data-mined and analyzed to look for long term trends so we could understand the processes better.

In that way, it's about control. But you're quite right, it's not about instant control, because if you ain't got it right, you ain't gonna get it right.

DR. LAYLOFF: As always. Okay, if we can

move on now. Have we identified--this is Question 4, on page 3: Have we identified the key issues--real or perceived--that can be categorized under the heading of regulatory risk or uncertainty, and do you agree with the current thinking on how these risks may be minimized?

DR. HUSSAIN: I think the way we sort of approached this is for marketed products with good compliance history, essentially within the known history problem. We believe the quality is good it's fit for intended use. I think I want to keep emphasizing that this is focused on improving the process and we are not questioning the quality of the product. So with that in mind, we sort of proposed that how we would address that.

And one of the main risks that is being identified by industry, as it happened today, also, is the risk of finding flaws in the current system. And what our position is the current system is fit for intended use. There's no safety and efficacy concern. So there should be a way to resolve that and then move forward and not be penalized for that.

And the point I--Dr. Woodcock made at the Science Board presentation was some of our current

testing could create that. For example, with content uniformity, it's a situation where no tablet should be outside 75 to 125 and on stage one, essentially, it says that when you test 10 tablets if the mean is between 85 to 115 and the RSD is 6.8 percent or less, that's acceptable.

If you assume that we normally distributed system, what it means is 6.8 percent RSD would actually we'll have tablets outside 75 to 125. And when you increase the sample size, then you will find those 75 to 125 and it means that every batch is out of specification, literally.

So what we are proposing is and the Science Board endorsed that--when we find something like this we will use a rational statistical approach for addressing that and not say this is out of control--so, my glass is out of control.

DR. LAYLOFF: Ajaz has become out of control

DR. MORRIS: If I could just comment, I think that goes back to something we talked about at the first meeting, which is reconciling the specifications from two different methods. I mean the errors that are associated with a PAT, as opposed to a malcompendial [ph] test may be

different, but if they map to each other in a statistic--and I'll leave this to the key mathematicians and statisticians, but then you're not out of specification as long as they're mapped. But I think that's the--that's the--I don't know what the word would be, biggest request on behalf of the industry to the agency is that that be recognized. That, in fact, when you do have tails of the distribution that we don't now see that not impugn the product. I think that's what it comes down to.

DR. HUSSAIN: Just to summarize for the committee. The current thinking is, the safe harbor concept that Dr. Woodcock has talked about. Essentially the way we have framed that safe harbor concept is that we believe that the current system provides product of good quality that is fit for its intended use. During development of PAT applications on marketed products, the information collected using experimental PATs would be considered as research data. Only approved regulatory tests will be used for product release and regulatory decision. So you would be--feel free to sort of collect that data and then we can find a way to--if there are flaws, then how we

would address that, but not be penalized for that.

DR. MORRIS: IS it audited, though still, is that data audited, or is that an open question?

DR. HUSSAIN: Not for agency purposes, it's research data, so you would use that for making or transitioning into the PAT application.

DR. LAYLOFF: I think the legal reference methods are going to be the approved method or the USP method, I mean that is the benchmark, that's what you operate from and if you have other data, it's not really relevant from a regulatory point of view, it's academic.

MR. FAMULARE: No--as part of a regulatory inspection, that wouldn't, you know, if you're doing--if your R&D facility normally isn't inspected and in terms of somebody's doing a post-approval GMP inspection, if you're doing R&D work on PAT that wouldn't be the normal course that an inspection would take you through. Once you implement PAT or PAT becomes part of the paradigm , you know then we have to look at it--

DR. LAYLOFF: Up close.

MR. FAMULARE: --from a reasonable perspective. And as Ajaz alluded to, if you're using a specification of content uniformity based

on limited sampling, then we have to have the proper guidance for our investigators and the teams doing these inspections that you have to see it through a different set of glasses. It's a different statistical paradigm. And the company, basically, the bottom line is the company is taking this for use of product improvement and we shouldn't do anything in our inspectional [ph] approach to hinder product improvement, otherwise, we've defeated the whole purpose of our inspectional program.

DR. SHEK: So, in practical terms, okay, if we're going into 4a, okay, where it says robust products, and a sponsor decides to look into use PAT and they found some various data there, you know, information. Is this data will be open now to inspection through, let's say a general GMP inspection and the question would come, have you done something about it? Here you have the data, and I would assume some concern might be there. And that's not R&D, now it's already in production, manufacturing, maybe it goes to a technical services group, to look are there are some findings there and it still passes, you know, the specs everything is there with the test, but we have some

findings which may be directing you to that you have to do something with the product.

DR. MILLER: And the follow-up to that, if I may, is that that was the discussion about safe harbor, all along. It was finding unintended results, has nothing to do about doing routine testing in a PAT environment for whatever attribute you want to define, it was safe harbor for unintended findings. And we're skirting or skating, excuse me, away from that point a little bit. And I want that to come into focus.

DR. HUSSAIN: No, actually, we are asking the question to you, I mean, the question is being posed to you. What is the committee's thought on the safe harbor concept in this instance? What we think is, in the sense, and I'll have Joe sort of answer, also, is to say that now you have moved PAT to a manufacturing line--

DR. MILLER: Right.

DR. HUSSAIN: --it's still not your primary method, you're still collecting data to see whether it's suitable and you're actually going through the validation process. Now, you routinely see a few more tablets which are outside, quote/unquote, "specifications."

The decision, I think what we will have--as we go through the--during the validation process of the PAT, you already have a validated process of the old method. That method will be used, so we're not using--so at some point we would need to meet and say, all right, with PAT you are seeing these defects, what are your new, either acceptance criteria based on sound statistical principles? So that your process is the same used before and after. So you really have to come up with a new set of criteria how to evaluate those numbers.

MR. FAMULARE: The existing regulatory paradigm, even going back to our previous subcommittee meeting, will remain sound, so we're not going to use that new data, now that it is online in the manufacturing area to impugn the percent as long as your existing validation and regulatory methods are working and doing what they are intended to do.

And as Ajaz said, what the next step would be, well now, you see this trend, it's not something for our investigators to report on the 43 or initiate some regulatory paradigm. It's something we may come back to you and say, okay,

where are you going now with the PAT and what will we do with this process?

DR. MILLER: I'd like to comment and, just for the record, with discussions that we've had externally at CAMP and also with Bristol-Myers Squibb, I would like this to go down as part of a definition for safe harbor. Application of PAT to a particular process product will be at the sole discretion of the manufacturer and I'll--don't write it down, I'll give it to you again, but just think about the words. The application of PAT does not necessarily imply that a critical parameter has been identified. The FDA agrees that a company cannot be inspected, held under unusual scrutiny, or be liable for regulatory requirements as a result of data generated during the PAT development and implementation phases. And if we need to write it on the board, we'll do that. But that's the beginning of where we are with safe harbor. And it goes to, again, this aspect of finding unintended circumstances.

DR. HUSSAIN: What I would suggest is in this instance, if you could just share that definition with all the committee members and that the committee could make our recommendations on

that.

DR. MORRIS: I think one point is that and in Ron's definition, as well, is that, obviously, any company sees dramatic excursions, they're not going to wait to be told to look at it, but during the phase when there is still a question of whether or not the implementation, as we talked about this morning, the implementation is proper, then you can get spurious results that, in fact, don't reflect the process and as we were talking about with Hank, is that the best way to find polymorphs is to scale up and the best way to find flaws in your sensors is to scale up, as well. And I think that's the spirit of the definition.

DR. MILLER: The follow-up is in the spirit of this is--these are approved processes, there is no question --whoops, likewise, Ajaz--there are not questions about the product or the process but, you know, technologies are technologies and Acts of God, so we need to understand that.

DR. LAYLOFF: I wanted to make a comment on the, you know, we have a discussion and that's very useful. However, I think it's important to know that many of these comments should be

submitted to the docket as public comment, you know, so that they're out on the docket.

DR. MILLER: Well, we appreciate that, but this also stimulates immediate thinking and challenging to our committee members and anyone during the two days. I we'll be glad to put that down in writing, very clearly, but it goes to the process of stimulation your thinking.

DR. LAYLOFF: No, the stimulation is fine, but send it in to the docket.

DR. HUSSAIN: Tom, I'm not sure, I mean, I'm not sure, the whole thing is sort of a public record anyway, so the docket, we had sort of a different thought for the docket was actually to get different type of information, so this is sort of a suggest from a committee member to sort of have the discussion here, and that's relevant to that.

MR. FAMULARE: Just to follow up on your thought, while PAT is developmental, you know, you have all those concerns, but you have the concern that Hank raised in his robust process where he gets this outlier at 62 percent and what does he do with it? Well, maybe PAT will help him, you know. So then, you don't want it one way, but we'll give

it to you the other way if it helps you.

DR. KIBBE: Let me just say that when we discussed this, we discussed the regulatory environment being empowering. And I think your points are well taken and I think we would encourage the agency's guidance to take them into account and empower the companies to try PAT out, to use it on a process and if, for some reason, it doesn't help them control that process well and meet the current standards, then we're not going to make them do it. All right? But I have a sense that some of these unforeseen boulders are going to be bumps in a process to a better environment all around and that, in the process, of developing a PAT if they find one of these things and they want to continue to forward, they might find ways around it, they might find cures for it, or they might find a way of correlating the data they get from their PAT to the data that they already get and say, all right, the standards on our standard testing is x and the standards for a PAT testing is you and the two are directly correlated, we still produce the same product, is that okay with the agency? And then the agency can go forward.

And so, while it's nice to worry about

things that might happen, we haven't opened the closet to monsters incorporated on this. I think we can go forward and I think we need to be clear with that. We are not going to force a company that takes the energy to look at PAT and try to develop something to implement it just because they're tried it. Okay?

DR. BOEHLERT: I just wanted to make one other comment. It's not unheard of now for the FDA to come into a company who think they have a product and process well under control and make comments on the acceptability of that process and it's controls. We're not going to eliminate risk here, you know, that risk is always there that somebody's going to take a look at what you're doing and say it's not what we think you should be doing or how you should be doing it.

The concern is that once you start working on PAT and you have data on hand now that confirms that observation, you know that the agency will not look at it as a safe harbor kind of concept, but look at it as, well, we could have told you that if we'd come in earlier, that you have a problem with your process. And you know that people are not going to want to generate more data that will just,

you know, be on hand to show that they do, indeed, have a problem. Because you may not think what they have now is okay.

MR. FAMULARE: But aren't--if there were to be an enforcement or any type of an issue it would have to be based on the conventional, existing paradigm, not what PAT did or added to it.

DR. BOEHLERT: Yeah, exactly, but having additional data on hand, may not help that situation, as far as the company is concerned.s

DR. MORRIS: I think one point is to--

MR. FAMULARE: I'm sorry, just to finish that thought. Then the company already knew it from the conventional data and this is what just icing on these cake so--

DR. MORRIS: And I think that was sort of the point I was going to follow up to your 62 percent point is that what we've seen is that processes that are fairly robust, at least in our hands even at scale at some point, certainly not as much as the, we haven't done as much full-scale work as the folks across the aisle, but typically are benefitted by the application of PAT. They reflect that.

And the processes that are on the edge,

everybody already knows they're on the edge, I mean, that's not a secret, so I think, to Judy, that's to your point, is that it's certainly not going to make a process that's on the edge look any less variable but, hopefully, it points out opportunities for improvement.

DR. HUSSAIN: To sort of re-emphasizing that we truly want this to be a win/win and the lack of trust and the lack of the history has been--and we have to rebuild that trust and as you go down the questions, you can see how we're trying to do that.

One of the aspects is, in the sense for PAT-based submissions, as we identified--that's the reason I was focusing on the definition is because we really need to distinguish PAT applications and inspections from the rest of them, because we are creating a new team which should be the only folks who are reviewing and inspecting these things and not anybody else. So you have, essentially, a new regulatory paradigm emerging from this. So, as you go down the questions you'll start seeing how we sort of intend to handle this.

So what the safe harbor concept simply is--it's a good compliance history, it's an

approved product, safe for intended use, there are no safety and efficacy concerns, most of the time and I don't expect, personally, to find any safety or efficacy concern. There will be concern of deviation from maybe some established specifications and that, I think we probably want to address through statistics, a more statistical approach.

And then, I think if variability can be reduced with the application of PAT, I think it would encourage companies to do that. And companies would, obviously do that. So that would be the sort of paradigm. So.

DR. MILLER: And that comes from the discussions that were held at the Science Board--

DR. HUSSAIN: Right.

DR. MILLER: --Janet and you were involved speaking to the statistical tails that occur so, you know, that's out there and we have to use PAT to potentially control that to a finer level.

DR. HUSSAIN: Sort of a personal point I'd like to make here is this --in a sense, I think, the zero-tolerance-type of limits that we have worked under USP and so forth. Keep in mind, USP is not a release test. USP's a market standard.

It was never intended to be a release test. So what it simply means is if somebody takes the product from the market and tests it according to the USP, you have to meet that standard. It's that standard, so, and so people sort of blur those things up.

At the same time, I think with the continued uniformity as it's outlined in the USP right now, we know if it's normally distributed you will have numbers outside that. And today, how do we deal with that situation? We actually throw away batches because it's out of specification and in some cases the quality the batch that is rejected and the quality which is accepted is no different. So, are we just feeling good about having a zero-tolerance and saying we don't want to deal with it? This is a way to really deal with the science issues underlying the whole process.

DR. MILLER: Ajaz, that also goes to the harmonization point, because there is some concern to the fact that, well, these products are tested as USP. So how does Europe or other countries or how will they accept potentially a product that doesn't have a USP test and then so it's an alternate test?

DR. HUSSAIN: You always have the USP test, you have that USP test.

DR. LAYLOFF: And the USP does not require that you test by the monograph. It says that if tested by the monograph, it has to comply. But you can use alternate technologies as--

DR. MILLER: Well, then it goes--I appreciate that, but it goes to labeling and nuances, I think--

DR. LAYLOFF: No, it just says, if tested, it would comply to the USP standards.

DR. HUSSAIN: There's no difference.

DR. LAYLOFF: I think we've hit most of the 4s, haven't we?

DR. HUSSAIN: The 4a, the question 4a was essentially saying that the statistical criteria, essentially the normal distribution and the inherent variability that we currently accept is one of the reasons for finding flaws.

Are there any other problem scenarios that would need to be considered for products which are in good compliance. I mean, that's the question. So, now we can go on to the next one, then. So, everything is right on target.

DR. LAYLOFF: We didn't much enthusiasm on

that one.

DR. HUSSAIN: Well, I think the question 4b, I think could be looked at from two different perspectives. One is that if we are able to say that it's a good compliance history, we don't need questions 4b, that's one way of looking at that. Or do we should consider 4b, I mean, that could be the way of addressing that. Because you will--may find something which should be corrected and then you really need to have a risk-base, not sort of use the penalty format, you say correct it over a period of time or something of that sort. A risk-based approach would be needed.

DR. MORRIS: One point on 4b, I think, is that, you know, there may be times when you try to apply PAT, say, to blending or something and there's just no correlation at all. In which case, you say, well, this is not the sensor or I haven't, you know, implemented it properly. That seems to be fairly straightforward. But it comes back to, then, if the industrial scientists make that call, then it comes back to the training of the reviewers and inspectors to recognize that, I think, as well. So, it's training on both sides, but to me that's an easier hurdle to overcome.

MR. FAMULARE: I think a lot of 4b would also be the use of enforcement discretion when these issues are found and what steps the company is taking towards resolving them if they are legitimate issues that need to be addressed.

DR. MORRIS: That's corrective action.

MR. FAMULARE: It's the step towards the--

DR. MORRIS: That's the other side, yes.

MR. FAMULARE: --which is part of the normal paradigm, you know, steps towards compliance is the most important consideration that we look at.

DR. RUDD: I'm sorry, I think I'm slightly behind. I think my comment relates to 4a, but it will be very quick. Just ready to re-enforce the fact that we need to recognize that we'll see statistically more variability as a result of the application of PATs and so, I think in terms of any training component, we just need to get a good understanding of what that additional variability might be. Don't have any answers to that, but I think it's just a recognition that, you know, the expectations need to change. Sorry for being a bit behind, there.

DR. LAYLOFF: Okay, I'm going to stop

this. Did you have--want to comment on this?

MR. CHISHOLM: Just the main thing that came out when I put these questions to people really was what we'd like from the agency is more of a definition of what--when I put this to a number of people and they said really the questions that come back are they would like the rest to be more specifically defined, I think, rather than generalities. What does constitute a problem, you know, I think there's a variable feeling in the industry that it's still a little bit willie [ph], although everybody's getting a very warm feeling about all the correct things that are being said. You maybe have to be slightly more specific. And I'm thinking, not so much of existing products here, as even for new products. It just goes back to Dave's point there that there will be statistical variations, which is something the pharmaceutical industry's never dealt with in it's life. So, it's not a yes or a no situation anymore, it's a maybe situation.

And we have to give some thought to that because it is a very risk averse industry. So, it's just a comment rather than a question, I think.

DR. SEVICK-MURACA: Yeah, I would like to see this issue of statistical variability along new PATs somehow being formally recognized in our guidance that, as new PATs come through, that there has to be a cogent scientific approach to saying when, you know, to handle the scientific--the measurement variability. And that's the thing that I'm really concerned about, because sampling sizes are an issue here, depending upon low-dose, high-dose, you know, there's going to be enormous ranges of variabilities, and these need to be addressed in how we're going to regulate and how we're going to put PATs into the validation concept.

So I think that we need to do some training on that.

DR. MARK: You know, maybe I'm showing my ignorance here, but I'm not sure what it means to say you have risk-based approach. Is that a standard pharmaceutical term or what's the meaning of it in this context?

DR. HUSSAIN: Well, I think, everything that is focused on safety and efficacy, most of the time we don't think there's a safety and efficacy issue. But if there is a concern with respect to

safety and efficacy, for example, we see a number of tablets at 60 percent and so forth, that the dose truly is lower for a drug, then a corrective action would need to be sort of worked with the agency and so forth, so there's a risk associated with safety or efficacy.

DR. LAYLOFF: Okay, we're going to stop this discussion at this time. We've invited a speaker from NIST to be with us this morning. James Wetstone, is going to tell us a little bit about what NIST does.

MR. WHETSTONE: Thank you, Tom. Let me get this thing going. There we are. Well, thanks again for the invitation. My name is James Whetstone, I'm the Chief of the Process Measurements Division, which is one of the divisions at NIST that's in the Chemical Science and Technology Laboratory; I'll speak a little bit more about that and, again, thanks to the committee for allowing me to take a few minutes of your time to tell you a little bit about what NIST does and how that might have some impact on process analytical technologies as they might be applied in the pharmaceutical industry.

First of all, these are some discussions

of what NIST does, what we think we do, how we do it, what our core values are, our mission and vision statements, I'm not going to repeat those. I think you all can read that about as well as I can.

We're a presentation of the Department of Commerce. Our mission is strongly oriented toward providing measurement technologies and standards for industry and government agencies. And we strive to realize our mission and vision and use our core values in order to do that.

NIST is a broad--has broad technological capabilities that run through a variety of industrial applications or interests all the way from electrical power where, you know, everyone has one of these things sitting on the side of their house and they're all traceable to the primary standards that are maintained, actually, by the electricity division just across the 270 here. One of the tall buildings you saw over there was our administration building.

All the way from electrical power to medical testing, dentistry, transportation of various sorts and refrigerants here means that some of the work that NIST has done in the past, about

10 years ago, accelerated the acceptance of the Montreal Protocols for new refrigerants that are not global warming materials.

This is an organizational chart of the organization of NIST. It's composed of a number of things, NIST, actually was derived from the National Bureau of Standards about 15 years ago. And there were some new duties that were given to NIST at that time. And those are embodied, really in three places.

One is the National Quality Program, Ajaz mentioned in his presentation of the Baldrige Award. And the Baldrige Award is administered by the National Quality Program. The Advanced Technology Program is a funding vehicle for high-risk industrial research activities. The Manufacturing Extension Partnership is akin to the Agricultural Extension Agent system that has existed in the U.S. through the Department of Agriculture for almost, I think, over a century, actually.

This puts technological expertise throughout the states available to, primarily, to small manufacturers.

These seven laboratories are what we call

the old Bureau of Standards. Those are the technical capability of NIST, this comprises about, oh, 80 percent of our total staff.

What I'm going to talk a little bit more about is the Chemical Science and Technology Laboratory, where the technical expertise is lodged that is pertinent to the discussions of this committee.

CSTL visions and missions are similar to NIST. Specialization has to do with chemical biomolecular and chemical engineering activities. What we try to do is enhance U.S. industries competitiveness and capabilities through the application of new measurement technology and standards. Part of this has to do with the assurance of equity in trade and, obviously, it impacts public health, safety, and environmental quality, also.

Our activities are really enunciated by these three goals. We have a measurement standards activity, which is a core mission responsibility of NIST. We provide--we, CSTL, provides standards in these areas, as I mentioned above. We have a quite extensive reference data activity that is centered on chemical reference data of various types and

biochemical reference data.

And then measurement science is that area of--that is the well spring of our technical capability. We engage in a wide variety of research activities that are aimed at ultimately improving the ability to make measurements.

This is just an organizational chart of the Chemical Science and Technology Laboratory, Bill Koch was supposed to be here today to give this presentation, but he's out of the country so I'm giving it. My division has somewhat more application to process analytical technology than some of the others, although all of them have some contribution to make to there.

And just to emphasize, that the way we're organized is really by discipline. So, if you look at this Analytical Chemistry is just what it says it is. Physical and Chemical Properties is just that, physical and chemical properties of both materials and chemical processes, primarily; some physical processes; Surface and Microanalysis Science is primarily world-class microscopy capability, all the way from optical to various types of charge particle-based microscopies.

We have responsibility for the kinds of

things listed here, these are the group names, we have responsibility for the national measurement standards for these types of what I call thermodynamic variables, which are, in many cases, intimately attached to the manufacturing processes, certainly that the pharmaceutical industry's concerned with.

And the Biotechnology Institute--or Biotechnology Division is--looks at biotechnological processes; structural biology is an important piece of that. And in that we have a collaboration with the University of Maryland and its Center for vast research in Biotechnology.

We speak of our programs in the terms of the industries that we try to serve with advanced measurements technologies and standards. Certainly health care is a pertinent issue today.

Our facilities, as I said, are mostly just across the interstate. You're certainly welcome to come. It's a little bit harder to get in the gate these days than it was about a year ago. But it's still not difficult. You might see this building as you go back down the interstate to the airport, that's our administration building. We have a facility, NIST has a facility in Boulder, as I

mentioned, there's the CARB facility which is just about five minutes away from here. And we have some facilities in Charleston, South Carolina, in collaboration with National Ocean and Atmospheric Administration.

What do we do? Well, we provide standards for a lot of different things. And what I'm going to do is run down this a little bit. I picked some of these things because I felt like that they would have application, perhaps, to this particular audience. Raman spectroscopy has become, certainly a process analytical technology that's widely used. Mel Koch here, from CPAC and Kelsey COOK from MCEC have organizations that are practitioners of that art and they're practitioners of those arts in industrial contexts and there's a fair amount of experience in having done that. Not in the pharmaceutical industry, but certainly in many others.

Spectrophotometry, athopical [ph] absorbency standards, I think there was some mention earlier today about the penetration of that particular technology into the pharmaceutical industry and what we do is to provide the absorbent standards for those devices.

Reference data, well, there's a lot of it, and I just put some stuff down here that was, I thought might be useful in this industry. Certainly the mass-spectrometric database is sort of a hit-and-miss product that's in just about every analytical mass-spectrometer that hits the street. It's sold through our office of standard reference data to most of the mass spec makers and they incorporate it into their software. It's updated about every two or three years.

And then, as I said earlier, we provide instrument calibration services for these kinds of things in my division.

Just a quick thing--one of the things that the industry came to us about three or four years ago was the fact that raman spectrometry is getting to the point that it is, as I said, a widely used process tool. We think there will be issues about the ability to look at the intensity response from one instrument to the next. The ASTM committee on spectroscopy felt that was the case, too. And so what we've developed is the first fluorescent standard that can be used to calibrate in situ raman spectrometers. It allows you to do a number of things; one, it allows you to compare one

process to another without moving the instrument from here to there. The first thing that we've done is the 785 nanometer excitation source is one of the most commonly used sources in industry at this point, so we decided to do that one first.

It will be available for sale either--certainly by September, perhaps, by now. I signed the report on analysis of this thing about three or four weeks ago. We intend to go to the other commonly used excitation sources and, as I said, we expect the impacts of this to assist the industry in doing comparative measurements in process control.

So, with that, just going to put this back up again. We try to work with industry as much as we possibly can, with other government agencies. Typically in a third-party, disinterested-party role and, certainly, welcome any kind of comments you might have.

I just thought that I might add a plug. And that's this plug. Mel is certainly a member of the IFPAC Board as is Rick Cooley, and Kelsey's involved and there's another--some other friendly faces here. I think Ajaz put together a session at the IFPAC meeting last year. This is the

International Forum on Process Analytical Chemistry. It's a place where you can go and listen to folks who have had a lot of experience in applying various types of spectroscopies, primarily, and to--it's beginning to be some sensors as those technologies are beginning to mature to process analysis and control issues.

So, with that I'll stop and thank you, again, for your attention.

DR. HUSSAIN: One, just to, NIST, I think, would be a very, very valuable partner to FDA in developing with respect to standards and things that will evolve. What we have been trying to do is link with NIST and, in fact, at the next meeting of PAT, we might offer an opportunity to spend a day and have a workshop at NIST on some more technical aspects. So that's something that we are considering right now. In addition to that, I think the information technology--standards for information technology also, I think, NIST can help us in that regard and we are exploring that possibility. So, thank you again.

MR. WHETSTONE: Thank you very much, Ajaz.

DR. LAYLOFF: I think, Ajaz suggested that we meet with NIST because they might be able to

generate standards necessary to provide calibration for various sensors.

And with that we will break for lunch. And we'll start again at 1 o'clock. Thank you.

[Lunch Break.]

A F T E R N O O N S E S S I O N

[1:12 P.M.]

DR. LAYLOFF: We have four people who have requested to make a presentation to the committee at the open public hearing. Dr. Justin Neway, from Aegis Analytical Corporation.

DR. NEWAY: And what's the magic secret to getting the slides to show?

[Technical Interruption.]

DR. NEWAY: Mr. Chairman, ladies and gentlemen, thank you very, very much for this opportunity to speak to you today.

My name is Justin Neway, I am one of the two founders of a company called Aegis Analytical Corporation. We're a software company based in Colorado area, near Denver and we make software systems, develop and supply software systems for pharmaceutical manufacturers, specifically.

What I'd like to speak to you about today in the 20 minutes or so that I've requested is to present you with a perspective that I haven't heard discussed yet, except, actually this morning, some elements of what I'm about to talk about came up. And I'd like to use those openings to illustrate a particular set of problems that I think need to be

taken into account with respect to what PAT does, in terms of bringing out guidance and implementation in the industry.

I've called my talk Implementing New Process Analytic Technologies: The underlying challenges.

And I'm speaking specifically about in the manufacturing area itself, rather than in process development or R&D. And there is a specific set of problems that I'm going to address today.

To get started, I'll give you a little bit of background on myself and the company so that you know the basis on which I'm making these statements. And then just to recap some of the benefits of PAT as we see them and I think as many manufacturing professionals see them.

I'll outline these challenges and rather than just leaving you with a bunch of whining, I'll actually attempt to tell you what I think can be done, both from an industry point of view and a vendor point of view and a regulatory point of view, to help these things converge and achieve the kinds of objectives that I know you have as a PAT subcommittee.

So, to start with is that I'm a trained

biochemist and microbiologist. I spent 15 years in pharmaceutical manufacturing in several different companies. And I became very intimate with the data environment associated with process development and manufacturing in pharmaceuticals and biotech.

After that, I started Aegis about five years ago with venture funding from the venture arms of GlaxoSmithKline, Merck and Aventis. By this time, I and my colleagues had made presentations and visited, essentially, the top 30 biotech and pharmaceutical companies over the last 5 years. Several different sites, several different organizations within each and we have a tradition of actually, convening customer advisory panels to develop requirements for our software that help us more closely address what the industry's needs are. So this is the backdrop for the statements I'm going to make.

You can see that I've been on both sides of the table, both as a user wanting to solve the kinds of problems that pharmaceutical manufacturers have and now actually being in the position of being a vendor supplying software to address those issues.

Now to quickly summarize what I see as the benefits of PAT implementation, they're pretty obvious--we've gone over them this morning. I would like to emphasize the two in the middle here, most particularly. Shorter cycle times and batch release times and moves towards parametric release. I was very pleased to hear the interesting new distinction coming up on parametric release being real time release. I think that's something that is extremely important to distinguish: the fact that there is a time element involved.

Okay, so we want to improve all of these things, we want to achieve those via PAT implementation, but what about today's failure rates, compliance, and yield problems themselves?

The challenge in quality compliance, I think, was outlined best in what I found to be Janet Woodcock's words earlier this year. U.S. drug products are of high quality, but. And we know these buts: increasing trends towards manufacturing problems; recalls; disruption of operations; drug shortages; negative impacts on NDAs; low efficiency manufacturing QA; slow innovation and modernization.

Why do these problems occur? Having been

in the manufacturing business myself, in the trenches, as it were, I know these people are not under motivated or somehow not trying to achieve these things. There must be obstacles and reasons why this is so.

And I think the obstacles can be summarized in this slide here and the two that follow. I'm defining here what I call data-intensive decision making. And that is where you need to make a decision for which you, first, need to gather data from various systems in your manufacturing operation that allow you to make that decision rationally.

Those decisions come up in two broad areas. One is in quality and regulatory compliance, GMP, in general.

And the other's in process control and stability. It happens that these are closely related, but it's often the case that manufacturing professionals don't necessarily see them as being closely related. When I talk about quality and regulatory compliance, I'm talking about parameter review for batch release; I'm talking about defensible specifications; investigation of atypical batches; manufacturing process validation;

production trend analysis; annual product reviews. You'll recognize right away that these are not something you simply sit down at your desk and begin to expound on. You need to gather data first and do investigational work, descriptive analysis and investigation analysis to be able to make good decisions about them.

On the control side we've spoken and heard much about that this morning: shorten process start-up times and scale-up times; shorten troubleshooting times; and reversing adverse events and trends; improving process stability; product quality and productivity. In general, improving return on net assets. These are things that all manufacturers want to do.

But there are a set of constraints within pharmaceutical manufacturing that make that particularly difficulty. What are those constraints?

Well, one of them is, in fact, what I term the real manufacturing data environment. To summarize it, we could say that the necessary data are located in many separate places. Okay, they are all over the place. And for good reason. Systems have grown up over the decades to supply

specific needs and specific parts of manufacturing and, as a result of supplying those needs, they've accumulated data about those needs.

Here I show a LIMS system, a SCADA PLC DCS-type systems; batch record systems. SAP would be the archetype of the ERP system. Many people have data warehouses that house subsets of this data.

But this data universe, you know, this environment serves an excellent purpose. It allow people to do their job of manufacturing pharmaceuticals and releasing batches. But it also presents a significant difficulty, because each time you want to do some kind of investigational analysis or data-intensive decision making, you often have to go to several of these data sources to get the data. And that, today, takes weeks--not days or minutes or hours, but weeks--in some cases, months.

And that's the reality of the data environment that I've seen first hand and worked in first hand.

Now when we speak of batch release and shortening batch release times. You've heard G.K. Raju speak about how much time it does take to

release a batch. Simply having a new probe does not speed that up. The data for a PAT instrument or several PAT instruments would accumulate in just one of these systems, typically.

Batch release consists of looking at conformance of parameters for raw materials, unit operations, and final product and the data for all of that resides across all these systems. PAT instruments are just one or two of the components required for batch release.

So, I can speak about, then, data--decision making inefficiencies. And I'm being generative here when I say inefficiencies, okay? There are problems, challenges.

It takes several weeks of manual data retrieval to be able to do the kinds of data-intensive decision making we've spoken about. And you can consider batch release, as I've mentioned, to be one of those decision making tasks; whether it be PAT-involving, or otherwise.d

What happens is what I've called spreadsheet madness. In general, vendors have been supplying customers with Excel add-ins, as a way of doing analysis, okay--or environments in which they're free to write any command line program they

like.

Well, as I mentioned, I'm a biochemist and a microbiologist, I don't happen to like writing programs. I hire other people to write programs for me. Process engineers sometimes like to write command lines.

But we find that quality professionals, process engineers, plant managers, supervisors, operators, in general are not interested or wiling to write command lines. They want point-and-click systems. And why shouldn't they have them. They're abundant in other areas of where we work today.

There's a bewildering choice of inadequate software. By that I mean that most analysis tools, most decision making systems have in fact, grown up to serve a general set of needs and they're being force fit into the manufacturing environment. What people need are easy access--meaning, point-and-click environment--to those analytical techniques that are most appropriate for the pharmaceutical environment for the kinds of data-intensive decision making I've described.

And, finally, the ways of communicating results, I find, even today are antiquated. In

general, tables of numbers vast numbers, lots of numbers where people have to do mental additions and subtractions are what people are communicating to one another. When we have so much computing power that three-dimensional imagery is easily accessible.

In fact, that leads me to a description of industry trends or some industry trends. There are plenty of new instrumentation coming along. Part of what we're talking about here has to do with that: cheap data storage; computing power; increased enforcements of GMP; patent expirations; industry consolidation and globalization is forcing companies to try to identify centers of excellence in manufacturing; reduce redundancies; and focus on specific manufacturing plants or regions of the world where they can produce the kinds of quantity and manufacturing efficiency that they want to do.

The technology already exists to adequately deal with the inefficiencies I've described.

And I want to give you just two examples of the kind of technology I'm talking about in a couple of areas. One is a feature extraction capability.

If you imagine for a moment that you have some probe, let's say it's a new PAT probe, it's measuring some signal as you see on the right that's triphasic. For proper release of the batch, and this is in a theoretical, okay? For a proper release of the batch, one has to define the rate of increase of the middle right here. Doing this needs to be as simple as I illustrate here. Point to the beginning of the curve, point to the end of the curve and get the software to derive the constants. Now you can release this batch if it, indeed, fits the specification for this centered rate of change.

To illustrate what I mean by improved methods for illustrating results. I give you what we call a visual process signature. In this example, the tall peaks are the ones that most effect the process outcome and I'm defining the process outcome here as the back peak on this surface which is dissolution rate. It's often the case we find, and we do work for people to illustrate this--that the parameters that most drive the process outcome are distributed across the process.

In this example, we've got an API

parameter; a mixer parameter; a drier parameter, and a coding parameter that all contribute the majority of the variability to the process outcome being dissolution rate. One or two of these might be a PAT, okay--technology or probe. The others are the traditional measures that span the process from raw materials. All that data still needs to be retrieved, made available and analyzed so that a batch can be released more quickly.

Okay, now we come to the wrap up? What's in it? The advantages of PAT. I see PAT as an excellent balance between compliance and economics. And we have before us, I believe, a rare opportunity to be able to drive change in the industry from an economic perspective rather than a disciplinary perspective. It refers more to the win/win that you've been speaking about all along Ajaz.

FDA wants better compliance to assure safety and efficacy. They also want better manufacturing efficiency to lower prices. The industry wants to comply, but they lack the necessary software capabilities, in general. And this is my assessment from my years of speaking to people.

They been building the cost of failed batches into prices. If only we didn't do that, presumably prices would be lower. And they want a shortened cycle time to improve process economics. Now, for this to work, the realities of the manufacturing data environment must be dealt with. What can we do about it?

From an industry perspective, I suggest boosting manufacturing IT spending. And I've underlined manufacturing IT because I think this is the area that needs encouragement from bodies such yourselves. There has been plenty of money spent on IT in general in pharmaceutical companies, but I feel it has been misdirected and not applied specifically to the manufacturing area as it should.

Include manufacturing users in budget prioritization. That means people who actually have to do with data-intensive decision making should be part of the decision making process in how those funds are allocated with respect to manufacturing IT.

And that, of course, would lead to implementing the underlying IT infrastructure needed for PAT. I mean these things just go

hand-in-hand. PAT, I think is not such a huge revolution when we look at what the trend industry has been doing up to now.

For vendors, let's make better software systems and work with the industry to define those needs as opposed to making broadly applicable systems that don't get well used in the pharmaceutical area. And let's be honest about software capabilities. Let's face it, Excel add-ins are not the way to solve these problems for people who want to do the kinds of analysis I've just described--and to provide better training and support.

On the FDA's part, continuing emphasis on the GMP compliance and outreach is critical. Because making a position clear that this is not a choice that we must, in fact, comply with GMP is very, very important.

Now, here's something that I haven't heard discussed that I'd like to really emphasize. And that is making opportunities--taking opportunities to emphasize positive PAT economics. And I mean, in very concrete terms. So, I'd like to suggest that data be gathered and that a very concrete ROI case be made as part of what this committee does,

to illustrate the very real economic benefits of shortening batch release times and product development cycle times. I think I've just heard about them in generalities up to now, I may have missed something, but I'd like to encourage a very concrete development of that case.

And so here's what I would suggest for this committee, if you'll forgive me for doing so. Continue the so-called safe harbor policy development. There may be a better term. Account for additional necessary manufacturing infrastructure. In other words, wide implementation of PAT, whether it be on existing processes or new processes will come to naught, unless we also develop the necessary infrastructure to make the whole thing work as I've described, because it's not just about that next new measurement or about the technology, in fact. It's about the whole systems approach that's needed.

Publicize compelling economic justifications, accounting for the hard costs, the soft costs, and the social costs.

Sponsor industry/vendor working groups to define needs, develop requirements and provide feedback. I would be more than interested, in

fact, more than willing to participate in forums under the FDA umbrella or this subcommittee's umbrella that specifically defines requirements for vendors with participation from industry, so that we indeed develop systems that actually are needed.

So, to summarize and conclude, PAT implementation, I believe, will be more difficult for the reason that it doesn't involve, simply, the next new probe. It involves leveraging other systems that I believe are deficient today in the industry.

The challenges are similar to those in other data-intensive decision making areas and that means poor availability of data. And by availability, I mean, real-time access to data, not weeks long and inappropriate software systems built for people who really aren't capable of using them very well.

A PAT provides a unique economic incentive for quality compliance. And I've talked about that a little bit. It's a way of getting industry to use their own inherent motivations to achieve the same ends as what FDA and this committee would like.

On the FDA part, I believe that it can be

a catalyst for vendor/industry cooperation. Gathering data to show the real world manufacturing environment. What I've given you today is really only anecdotal, but it is my direct experience.

Publicizing the positive economics of PAT and providing the forums for interaction between vendors and the industry.

Thank you very much.

DR. LAYLOFF: Thank you, Dr. Neway. The next presentation is by Lie Peckan and Allan Wilson.

MR. WILSON: Good afternoon, my name is Allan Wilson, I'm with a company called the 20/80 Group and I'm an automotive manufacturing guy, is what I am. My background's in chemical engineering and statistics, but I came here today with my partner, Lee Peckan, who handles human change management in the automotive industry, which is another interesting thing to talk about all together--to talk about what we consider an interesting topic. And I hope you'll consider it, as well.

We've been involved in the transition and transformation of the automotive industry. Myself for a little longer than Lee, around 20 years. And

we've begun to be involved in the pharmaceutical industry, for the last year. We've done a little bit of work here and there. And we find some really interesting parallels in the changes that have occurred in the automotive industry over the last 20 years and what you're undertaking--you're already undertaking and you're going to be doing moving forward, I believe in the next decade.

So the first question is why the comparison. Now, the obvious thing is the automotive industry has gone through some very unpleasant transformations and a lot of those transformations were very hurried and they were forced as I'm glad to admit, the automotive industry is not a monolith and we've been extremely susceptible to the flavor-of-the-month thing. Like, you know, if I were to rhyme off the number of little certifications and qualifications I hold in this and that it would be kind of terrifying. You have an opportunity, I believe, to take a more--a more measured look at your industry and take advantage of some of the learnings that have gone on in other places in the universe.

So the first thing is what happened to us back in 1980 in that time range? Basically three

things happened. Three really unpleasant things happened and they happened in concert. Basically, we had problems around pricing, quality, and foreign competition.

The first thing is pricing. This is a chart that I picked up from public sources. This is the cost of crude oil over a relatively short period of time, sort of centered around 1980. That, in combination, with the fact that this is kind of what the typical car looked like at that time, as a matter of fact this looks very much like my buddy Don's Duster and it was actually a small car at that time and very fuel efficient. And people began talking about these things, you know, as these terrible gas-guzzling dinosaurs, so the domestic automotive industry began to come under all kinds of unpleasant pressure to find more fuel-efficient vehicles.

At the same time, just in case lack of fuel efficiency wasn't bad enough, we had some really significant quality problems going on, of which this was probably the most dramatic incident. You know, those of you who remember Ralph Nader. But there were all kinds of other things, basically around product quality.

So at the same time as we were seeing issues around cost, around product quality, began to be a ground swell in the so-called consumer culture of North America to change cars. Just in case life wasn't bad enough, along came Toyota. I still have a hard time saying that name, sorry.

And what those--what those scoundrels did was they delivered good, fuel efficient cars. And it really--it really shook us up. And we had to make some very significant changes and very painful changes. And in some cases very hurried changes, relatively speaking into a North--to the domestic North American automotive industry.

But when I think about the changes that have happened, consider this and sort of contrast this with the situation that you find yourselves in today.

Think about the typical automotive assembly plant that makes cars. What I'll call a mini automotive assembly plant. Twenty years ago, a typical automotive assembly plant would make about 800 cars a day.

Nowadays, a fast one will make almost 2,000 cars a day. At the mean--in the meantime, that same automotive plant, which used to occupy

around 2.5 million square feet, has gotten much smaller. Actually there are plants coming off the boards right now that are under a million square feet, which, considering the amount of activity that goes on is quite astonishing.

At the same time, that work-force number--those are the number of people who, basically have to clean up messes. The kind of people who go, well, here's a car, oh, my goodness it doesn't work. We have to do something to it. And there used to be hordes of people at the end of the typical assembly line who had to fix things gone wrong. Hundreds on a given shift, 500 would be a typical number. Now, there are very few of them.

At the same time, that's product warranty, things gone wrong in around, you know, a three-month time frame. Then the things gone wrong have dropped, by over an order or magnitude. So, basically, when you buy a car today, you don't expect to have nearly as much trouble to have to take the thing back to the dealer by an order of magnitude as you did 10--well, actually, 20 years ago.

On-site inventory, these are basically the

parts being held at a main assembly plant. The on-site inventory levels have dropped, essentially, by an order of magnitude. And, similarly, the incoming quality problems from vendors, because as you can imagine, you buy all kinds of bits and pieces to make a car. And there are very complex vendor chains. The incoming quality problems have decreased by two orders of magnitude.

So, I would ask you to consider two things, okay? The first thing I would ask you to consider how much, the car you drove here today with air bags that weren't there before; antilock brake unit, wasn't there before; an engine that you don't have to change the spark plugs for 100,000 miles, that wasn't there before. And how much that car would cost if this hadn't happened. Quite, it would be astonishing. Actually you wouldn't be able to buy that car. That car would not be able to exist because people wouldn't be able to afford it.

The second thin I would ask you to consider, is what would happen if you were able to trust your vendors more by two orders of magnitude. Or if you were able to run, basically, five times as much material through your existing

Cyber-licensed facilities or CDER-licensed facilities, without having to--like I have a fair idea of the costs associated with licensing new manufacturing facilities in the pharmaceutical industry. That's the kind of transformation that the automotive industry underwent. And I believe that you're on the way to experiencing similar transformations.

Now, what I would like to do, once again, the automotive industry wasn't a monolith or anything, but what I'd like to do is, I'd like to hit upon six--six major changes that happened to us and it's the kind of thing that you can only look, at with the benefit of 20/20 hindsight, you know, because at the time it was kind of messy, you know. Like when Iacocca blew up that assembly plant on television, we all cried for three days, it was kind of unpleasant.

So, think about these, basically these three things. The first thing that changed is the understanding of what our customers wanted. The perception of who our customers were and what they were willing and happy to pay for. And we realized that the pharmaceutical industry already has a very strong understanding of that but the FDA is

essentially a customer of the pharmaceutical industry. And how does that relationship play out.

The second thing is to be mindful of your competition. Know exactly what your competition is doing and I think that this is, for instance, a marvelous forum to drive a certain amount of standardization in the industry. The automotive industry is the most benchmarked industry on the planet. There are people benchmarking everything imaginable about automotive. And I think that's a very good thing.

Develop a strong focus on product quality and finished goods quality, which you already have obviously, but that was actually needed in the automotive industry, because the '50s consumer culture said anything you can make people will buy. So we actually needed to develop that an understanding of what our customers were willing and happy to pay for.

But these final three things, I think you actually, I think may be of more use to you. When I looked at the--at the situation in your industry, I said, well, what's your product life cycle? Basically, to simplify it, how long is a product in production and a typical number might be ten years.

In the car business nowadays, a typical number is three years, but despite the fact that a given product is only actually made for three years, there's an absolute flurry of continuous improvement activity going on through that full three-year period of time, right up to the point where you stop making a model. You continue to improve it. And the reason is very simple--it's very simple because those improvements don't last just the life of that particular model, those improvements are fed back into design, development, and the launch process for the next models.

So you have a marvelous opportunity--a two-fold opportunity if we can find to make continuous work in your part of the world. Because, first, you have very long product cycles, so anything you can do to improve the quality, the reliability, efficacy that lower the cost of the products that you make, you'll have a huge period of time to realize the returns on that. So from the manufacturer's point of view, as well as the customers' if a way can be made to achieve that that will be extremely good. Plus, you'll be able to feed that forward to future endeavors.

The second thing is a focus on integration

of effort. Car companies are big. Car companies are extremely big. Car companies have many vendors and suppliers who are also extremely big. Each of those entities has functional groups in them--manufacturing, quality, engineering, marketing. In the evolution of the automotive industry of a greater working together type of evolution has come around in mechanisms of actual structures to manage the life cycles of products and to speed the life cycles of products and to actually force collaboration between functional organizations has come about in the automotive industry.

And I believe that that would be of great value to this industry, because, to start with, it's a huge industry, the companies are very large; the regulatory bodies are very large; the supply base is very large. And that integration of effort, in conjunction with improvement can be an extremely powerful thing.

The final element on this list is a redefinition of mass production. Henry Ford invented mass production so the automotive people thought they had it down cold until Toyota re-reinvented mass production and we like to think we've re-re-reinvented mass production over the

last decade. And some of the key elements are elements that you have been talking about today, elements around understanding your processes; around process as well as process quality; around understanding the quality of the raw materials and designs that go into the products that you prepare; and, also, an understanding around error proofing of those processes and those products so that the likelihood of problems arising on an ongoing basis are drastically reduced.

And those are messages that I would like to carry to you from the automotive industry. If those things are possible; that they seem expensive, but the payback is huge because of the time that's working in your benefit, especially with the large, at least in certain areas, the very large product lifetimes that you have available to you.

Now this is just a brief slide around our perception about the similar things that are arising in your industry to what we saw, say, in 1980 in the automotive industry. We see pricing pressures; we see pricing pressures, especially in the United States around government bodies, HMOs, PPOs. We see the issues or regulatory pressures in

your relationships with regulators. Those are pressures will continue. We see patent protection pressures, you know, the current paradigm around the expected life cycle of a product and the number of new products entering that life cycle pipeline. There seems, from our outside perspective, to be growing issues around, basically, the number of new drugs that are being launched at any given point in time and the ability to bury the R&D costs.

And we would submit to you is that manufacturing can give you so much more in terms of resources to then plow back into your R&D.

And, finally, foreign factors. You don't have a Toyota, thank goodness, but there are issues around the relationships with foreign regulators and with manufacturing in various points in the world and the need to harmonize and balance those things.

So this is our current thinking. I guess it's a little more specific around PAT, the prior stuff was rather general. In PAT, I see, basically, four issues that are challenges that need to be considered. The first is around learning to manage large volumes of data. And from a statistical perspective, there's an astonishing

pitfall that awaits you and, I guess, we could, anyone who wants to talk about the technical details later, we can, but SPC is actually a survey sampling tool that's applied to manufacturing. If you do large volumes of sampling and you apply SPC parameters, which we had the unfortunate experience of doing, you basically drive yourself nuts.

Imagine your typical SPC run real paradigm says that you can have, I guess, a false out of control signal about 30 times in 1,000 by the time you stack up the run rules. Well, that's okay, if you only sample every shift, like Shoehart did in 1930 at Western Electric, but if you sample 1,000 times an hour, as you're likely to with PAT, then you'll need a different mathematical approach to handling that data and not basically drive yourself into a tizzy, which is something we experienced.

The whole measurements systems thing and I believe that you're already addressing that very well, but your measurement systems have to be reliable, they have to be accurate and a great deal of energy in terms of development and in terms of mathematical development and effort has been expended in the automotive industry around our measurement systems in order to understand how

we're doing and be able to react in real time.

Process understanding--this really resonates with the discussions that you were having this morning. Process understanding drives the appropriate application of all this because if you don't know what to measure, then you're going to dump tons of resources into measuring things that you actually don't need. You'll expend these resources and you will needlessly chase ghostly images of poor product quality, so good product knowledge is, of course--and process knowledge is at the core of all this.

And, finally, one thing that I was very excited to hear this morning, was the notion of simplicity and parsimony in all things. There's a temptation that we fought in our industry for the last decade that's been brought about by the amount of high speed data acquisition equipment that's become easily available, relatively cheaply available, Sensor SCADA, so you find yourself able to measure all kinds of stuff and not necessarily knowing that you're getting value out of that volume of measurement. So, simplicity and parsimony and making systems such that errors are unlikely to occur, are extremely valuable. And the

whole discipline of error proofing and pokeyoke [ph], which, once again, is a bit of a technical specificity is, I believe, of extreme value to the pharmaceutical industry.

So those are our final comments. Basically, that we believe Process Analytical Technology is an important step on the, I guess, what you might call the quality journey of the pharmaceutical industry and we believe that this is an excellent thing. Thanks.

MR. KLEVISHA: Thank you very much. I'd like to introduce myself and a colleague. My name is Dan Klevisha, I'm the vice president of Bruker Optics. I guess, in terms of PAT, you can think of Bruker Optics as a sensor supplier--a vendor supplier of sensors. My background is not in pharmaceutical analysis and production, but I believe that some of the experience of our companies have applied in different industries are relevant to PAT and justify this initiative. And our presentation will be in two parts, Tom Tague will present a second part. Tom is a senior applications chemist at Bruker Optics, in Massachusetts, and he'll discuss some of the strategies for partnering for development of new

technologies.

So, I believe that it is very apparent and has been said several times quite eloquently that the PAT initiative is extremely important. I think you can take lessons from other industries and, certainly, apply it to the potential of PAT. Certainly in the chemical industry, the polymer manufacturing area, Process Analytical Technology was initiated and implemented as an innovation and a way to improve profitability and it has moved from that to being absolutely essential to compete in today's global market. And we see many examples in industries outside of the pharmaceutical area where I could call it the PAT equivalent application of Process Technologies have taken chemical companies that used to introduce a lot of off-spec material to the point that they've eliminated off-spec material creating an opportunity for the payback and return-on-investment of one in two months, in some cases.

And in other cases where the testing for analytical services for the polymer industry has been reduced from maybe 20 technologies down to just a handful of technologies that could be

administrated to a whole plant by just a small number of people. So there's certainly a lot of opportunities for a great deal of cost efficiency in manufacturing.

The aspect that we would like to very briefly touch on is what is a vendor and the essential nature partnering to achieve the goals of rapid and efficient PAT. I think you can kind of break down many of the opportunities of PAT sensors into the application of what would otherwise be established technologies, such as Newark Thread [ph] for online driers and blenders and content uniformity measurement equipment that's been well used in laboratories and even in some process situations but is not nearly fully exploited to the potential that is available to the pharmaceutical market.

So these are more or less existing technologies that can be applied on a greater scale in, perhaps, innovative and unprecedented ways. And there's a whole area of new technologies that simply haven't been possible before and both present good opportunities for the future of PAT.

Our company manufactures vibrational spectroscopy equipment near infrared, mid-infrared

and Raman equipment. And these technologies are highly applicable because of their nondestructive nature, real time analysis and applicability to a wide range of processes. So we're viewing this as somewhat narrow in terms of spectroscopy and specifically vibrational spectroscopy in terms of all the technologies but, clearly, there's opportunities across all aspects of pharmaceutical production for vibrational spectroscopy technology and other analysis techniques. And I think that's well understood within this expert panel here, so it doesn't need to be reviewed.

If you look at the paradigm of the polymer and chemical industry, you can see that a lot of the historical usage of process equipment was in the area of liquid analysis. Take a fiber optic probe and put it in a liquid stream or reactor, bypass line, something like that. And in the near infrared for raw material testing, techniques have been widely used. And those limitations, in terms of use, have been widely expanded over the last few years and I think will continue to do so with the possibility of putting, for example, fiber optic probes in blending and drying operations and the possibility of using non-contact analysis, in this

case an FT-NIR system configured for drying measurements and being able to measure solid-phase materials very rapidly online has greatly expanded the use of online technology in other industries, and including in the pharmaceutical industry.

There are a whole range of tests that are conducted on a laboratory basis that can potentially administered online and to measure much higher volumes of materials and much more precise analysis than has been possible before and Tom will touch on some of that, including the administration of equipment that previously was limited to laboratory use, such as FT process Raman and now is readily available for use in a process environment.

One of the challenges, I think, going forward, with respect to regulation of PAT is how do you take all the various existing issues of how do you get equipment that does the analysis that's required to eliminate the need for more laborious, slower analysis and chromatography titration to what chemical analysis and implement all that in a way that can be compliant with all the regulatory requirements, such as 21 C.F.R. 11 and validation and IQOPQ and things like that.

And much of that requirement for

instrumentation translates to the PAT environment but potentially gets more complicated and more challenging as equipment runs at real time in more demanding environments.

The--I mean, some clear aspects of PAT is that this needs to be a very broad-based technology usage and that I think you can almost--maybe it's not too strong a statement to say that some technologies are going to be more of an evolutionary implementation where they're already in use and understood and they're going to be used wider scale for process and there's also possibility of some fundamentally revolutionary stuff in terms of the instrumentation and the benefits that can be received from manufacturers in the pharmaceutical area.

So, I think I'd like to, at this point, turn it over to Tom Tague who will discuss a little bit of our concepts and strategies for partnering with new technology development.

MR. TAGUE: It seems like, to me, over the last 10 years or so when I've been involved with instrument manufacturers as a scientist, that the instruments are pretty much developed according to what the vendor tries to look at the industry and

says, well, this instrument could be helpful and then we go through a two- or three-year development process and develop that instrument and then, kind of throw it over the wall and then in the pharmaceutical company you are kind of left with, okay, is this technology useful, is this instrument useful or are you trying to evaluate all the instrumentation that's available out in the market and say, how can I fit this into my program--into my quality program and--or is it too much work? Is the barrier too high.

And one of the things I hope that can come out of these types of meetings is that we have a mandate where pharmaceutical companies and vendors will partner together to so that the implementation of technologies takes place such that item 1 doesn't happen where you spend a lot of effort to work with a product that has been on the market for a few years and then, all of a sudden, a new product comes out that makes the technology that you just spent a couple of years incorporating into your own business is completely obsolete.

One of the things that is also very interesting from a vendor's point of view is to be able to partner with pharmaceutical companies and

other manufacturers so that we can develop new technologies and new products that will not only help you, but help many different industries. And I feel that you, certainly, have the attention of all the vendors. And Bruker is, probably a good example and you could probably line up 50 different manufacturers and get the same exact words that we would be very excited in partnering and be willing to go that extra mile in doing so.

For Bruker, our business has changed over the last five years, in that, when we do development, we certainly have GMP, GCP, and GLP in mind as Dan alluded to. Our packages--all our software packages and products are intended to be fully 21 C.F.R. 11 compliant and that's through out interactions with you as being our customers.

And the 21 C.F.R. 11 compliance, I would say, for Bruker, is maybe the first example for us where we worked very closely with a few pharmaceutical companies to find out exactly what you wanted. Documentation was an issue, where at first we thought we could provide documentation that was always about 50 pages long and didn't really have the detail that was necessary and the end result, now, are very thick manuals that are

very comprehensive and can withstand the most stringent evaluation by the FDA or, more importantly, by your own internal regulatory affairs people.

So we want to provide comprehensive support for achieving your validation and your monitoring goals. If we produce a product that can't be used in your laboratory because it is not compliance, then we've defeated our own purpose and we've not--and we've wasted your time. So software compliance and documentation are big for us.

One of the examples that you can look at to is trying do direct analysis of a reaction vessel, where, in the past you have to swab the vessel and then do an HPLC measurement. It can be a very tedious process and it's not a very efficient process. It can be tedious, is not really quantitative in nature. We developed a product here that is pro-base, where you can just go ahead and get the answer for how clean the reaction vessel is right away.

I wanted to emphasize the next few slides in talking about microanalysis. This is a really good example as to--with the ways things are and have been developed in the past, and to where they

can go in the future.

The first is this little compartment, FTIR-based microscope. It's really good for identifying materials, compounds, contaminates, anything small, down to about 20 microns; takes up very little space; it is--works into being compliance with the instrument. You just observe the sample and do reflection or ATR data collection on it and it works very nicely.

But the next step might be to take this type of product and integrate it into a rugged, interferometer that could be taken right at line and be able to solve problems for you very easily.

This is an example as to what it is capable of. These are microbeads and you--there's some dark field illumination there and you can see, if you're familiar with infrared spectra, we're able to very nicely differentiate between the two different microbeads. Very easily done and the spectra collected in a matter of a couple of seconds.

Then we have a more research-oriented microscope and, again, this is an example of where this is a research tool that could be brought more into the manufacturing environment or many of the

features.

Where you have very advanced visualization capabilities of a sample and then pretty much any mode of analysis to look at monolayers to doing ATR spectroscopy or transmission. And you have full data processing at this level, you can do chemometrics on--full chemometric analysis on a very automated way on the data that you might get. And this is just kind of representative of the tools that are provided by many vendors where they're research oriented, but it's through a partisanship that they could be brought into the manufacturing world.

This is just another example of the next stage up, which incorporates a lot of different automation features into the product. And I'll skip over that one.

The next item is chemical imaging and the reason I wanted to go through these last two examples is you can see in our own products where there's been an evolution, just as with PAT, there will be an evolution as to what can be implemented in how the collaborations, at least, from the initial stages will go forward. And, in this case, you can collect the data over a very large area, it

may be as big as 6 mm by 6 mm in just a few seconds. So now you can talk about looking at the homogeneity of a tablet in a very short period of time.

And you're essentially only diffraction limited now, and you can perform chemometrics over the--globally over the whole data block. Someone--the previous two speakers have spoken about manipulation of data, this is a really good example as to what can happen.

You could take one of these imaging systems and put it right at line and look carefully at a tablet. The problem is that you can generate 100 megs of data with one--in one acquisition in six seconds. So how do you manage all that data? How do you get the information that you want out? There has to be partnership for how to get the answer without creating gigabytes of data in seconds.

This is an example of looking at a bone tissue. So if you wanted to monitor therapy and that was the purpose of this investigation. You can see visually the bone tissue and then look at the infrared image.

And then spectroscopically speaking, you

can get at the information that you can't get at any other way and that is, if you look at bone modeled after two versus that of one-year, you can see that due to--in monitoring the amount of carbonate, which indicates the degree of mineralization in the bone, you can see the changes very nicely and you can see the changes over the whole tissue of the bone in the same manner you would any other large sample.

And then you can look at the chemical profile and, maybe this is one of the most useful parts of doing imaging and the numbers on the bottom are small, but those are microns from 0 to 660 across the bottom. So we're talking pretty small spacial resolution but getting a lot of detail. So, in this case, if you were trying to--in another case if you were trying to look at a tablet, you can, again, imagine that you have a 6 mm by 6 mm area and gaining this type of spacial resolution to find out how good your manufacturing process is.

And this technology is available today and it's available from more than one company. And yet I fear that it may be many years before this type of capability is implemented.

This is what it may--one rendition that we offer that certainly does that type of job. You have a macrosampling area, you can envision a tablet hopper where you run tablets in there and then, ultimately, I think--this instrument is not capable of it because you're talking about 1,000 tablets a second instead of a couple seconds per tablet, but I think that, from Bruker's point of view, and from the information we're getting, everyone would like to do every tablet. And so, with close partnerships, that's the type of information that can prove very valuable. In this case, we used state-of-the-art FPA detectors and video cameras to take care of that job.

Another interesting application is just, kind of looking at using FT-Raman analysis and saying, okay, how easy is it to look at raw materials? Well, you can look through vials and bags in the Raman in--with near infrared excitation, so your raw materials identification can be done very, very quickly. I've worked with a couple of pharmaceutical companies over the last few months at looking at these things and you can identify with unit efficiency, raw materials in a matter of just a couple seconds. So, it needs to

be done and can be done.

This is another example of mapping the surface of a tablet using Raman. It can be done many different ways, you can monitor the concentration of aspirin very carefully. You can--let's see--I'm not sure why my Microsoft software's not showing that figure very well.

DR. HUSSAIN: Tom, we need to go on to--

MR. TAGUE: What's that? Okay, I'll skip over that. Essentially, you can look at cross-sections, as well as the tablet itself and also the degree of hydration on the tablet surface.

And, lastly, we also offer other products that are good for cellular analysis and bacteriological analysis and the detail that we've gone to, even here, is that, for example, with E. coli, we can readily identify in just a few seconds, almost a hundred strains--different strains of E. coli, just by streaking the bacteria on the zinc celinide [ph] plate, popping it into the spectrometer and getting the answer right out.

And, in conclusion, I think the future of PAT is bright, if people take action and the partnerships actually do take place. I think all sides are motivated. The FDA has called these

meetings and appears more than willing to facilitate collaborations to--so that the manufacturing processes can be more efficient, more cost effective. And, certainly, the--I think you'll find that the vendors are fully motivated. And I thank you for your attention.

DR. LAYLOFF: Thank you very much, Dan and Tom. And we'll continue now on our questions.

If we could go back to page 4, I'd like to start back with Question Number 4c: To minimize or disputes should a priori criteria be developed to assess if a problem uncovered during PAT implementation was present all along during the prior manufacturing history of a product? Page 4, number 4c.

DR. MORRIS: Just a question of clarification, I think, Tom. When you say a priori, does that mean that the data already exists from the compendial [ph] testing to show that there's a problem? I'm not sure--

DR. LAYLOFF: Seem to have criteria established before you find the problem?

DR. MORRIS: But, I guess, because my next, because it comes down and says for current products that need improvement being considered

case-by-case. But I'm saying--I guess I'm confused as to what criteria we're talking about.

DR. HUSSAIN: Let me try to clarify in this instance. I think, since we have heard so much about finding flaws--I mean, everybody seems to be saying that we will find flaws. And I'm sort of looking forward to saying that let's maybe define some criteria whether something is a flaw or not a flaw, you know. When you start with a product and a good compliance history, is that enough to say, that's fine. Whatever is there, availability is observed is fine. Is that enough or should we try to do something before to have potentially avoid any disputes or disagreements?

DR. LAYLOFF: Set a threshold for the dispute?

DR. HUSSAIN: Yeah.

DR. MARK: Well, during one of the breaks, we got into a discussion with some of the other people here and brought the question of, well, suppose one of these process--I guess maybe sort of jumping the gun on this question, but in response and discussion on some of the earlier questions, the questions came up, well, if something shows up because you applied the process analytical

technology, what is the company going to have to do about it? Are they going to have to jump on it right away and put a priority over all their other projects that ar going on? Are they going to have to put it in the stream of research projects and take care of it in due course, considering that they have been manufacturing this product, you know, in what was considered a satisfactory manner until then? And that's probably going to be an important decision that's going to have to be made in terms of the guidance as to what's going to have to happen?

MR. FAMULARE: I'm sorry, I think it's a decision you're faced with under the current paradigm when things become revealed to you that there's a product, whether PAT gave it to you, whether current validation and conventional testing gave it to you. You know, we touched on in question 4b, risk-based and what does that really mean, in terms of the application of GMPs and problems uncovered during PAT R&D efforts. And, again, as a company that's responsible, maybe risk-based wasn't the best term to use here, but when FDA, for example, sees a problem, first of all, it has to pass the, well what difference does

it make question, you know, Does it really make a difference in the process or is it a just sort of a specification that maybe we could re-evaluate in terms of whether it's in the application process or whatever.

The second issue is, what is the public health impact, maybe, as opposed to saying risk-based? If we see products that don't meet their legal specifications, they're in violation. We have ways of dealing with that. If it's a minor issue, the company comes back with a corrective action plan and it's the timing of it is appropriate to the meaning of the violation, or if it does have an effect on public health impact.

If it's a violation that may cause them to question the prod being on the marketplace, we have a criteria that we look at as to whether what the public health impact is and should it rise to the level of a recall? There's different classifications of recall. So, I don't think it's a new paradigm, I just think it's another factor that goes into that paradigm.

DR. HUSSAIN: It's not a new paradigm, but there is a difference. The difference is under the current system, the product has no compliance