

happened, because you did just three runs, maybe, to some extent; because there's a paper trail, there's a lack of access to all information in the same place. You now have to find out why you had that exception, and you have to have the same amount of rigor whether you're going to use it or throw it out.

You now have to say why you got an exception, you've got to say which lots it happened to, why it happened and what is the probable cause, and there's a significant additional time taken for that. And as I looked at that, I said, "Okay, it was the Pharmaceutical Manufacturing Initiative. Maybe it should have been the Pharmaceutical Testing Initiative. But maybe it really should have been the Exception Explanation Initiative, because the consequence of explanation initiatives shows up in the "So what?" category.

If you look at all these times on average, and you look at how much of an impact does that make, you say the average cycle time is about 100 days; the cycle time, standard deviation, is 100

days, which says if you're talking about 6 sigma, that's a lot of cushion that you have to build in. And exceptions increase variability by 50 percent, increase variability by 100 percent, on the average by 50 percent.

So when you told the vice president of manufacturing, "Just don't screw up." "Don't come in the way." "Never have too little inventory." "Don't stock up," what does he do? He builds a plant about 10 times bigger than he needs, about two years earlier than he needs, and he deals with the consequences for the rest of the 12 years. And as we measure the numbers, they show up in these places.

We need to have a fundamental technology: one, on-line sensors, but not only just LIF and NIR, but a way to look at these exceptions in a systematic way, and that's the next technology opportunity as well.

Let's try to look at asset utilization numbers in a manufacturing sense, very similar to what I showed you, so that we can understand where

the time is being spent. Just like we said "So what?" around on-line technologies, we said "So what?" around routine manufacturing.

Again, since we have a consortium of companies, we collect from the batch records all the detailed process steps, and we capture all the time spent in every batch for all the batches ever made, and we figure out how much time is spent by the operators versus testing, versus non valued versus value-added, and here is the first process that I showed you in terms of its time.

We started this batch, and we say, "Let's start pharmaceutical manufacturing given a start date, we're now in the market, and see where is the time being spent." And you can see the physical product, which is the round product right down here, and the paper product which is the square product going along with it, the so-called batch records. And you can go inside any one of these steps and you can say, "Where is the time being spent?"

And you can say very quickly the physical

product goes through, the paper product takes a long time, because somebody has to sign, has to figure out that they did what they're supposed to do, and the technology opportunity there would be the electronic batch record opportunity. That's number one.

We can now go inside the lab and figure out what tests we do, and we can say here are the different tests we do, the appearance, color, fill weight, and these are very solid, nice tests that have been in place. And we look at the bottom line drivers within those tests, such as the assay test, and you can find that it's the on-line nature of those tests that is going to impact those tests, and you can see that many of the paper and physical aspects of it drive today's performance.

As I started this simulation in the beginning of June 1997 in this case, let me figure out where I am, because if I got a batch at the end, I would get a number bigger than zero. It's about a month now, and I haven't got a batch out of the other end. Let me try to figure out where

those batches are.

DR. WOODCOCK: Can you clarify, these are real numbers?

DR. RAJU: Yes, these are real numbers.

DR. WOODCOCK: From a real manufacturing plant?

DR. RAJU: That's right, yes. These are real numbers from the actual manufacturing plant.

And you can see that we just got our first batch out and approved. In the meantime we're collecting finished goods inventory at the end, based on the real numbers, and we're trying to figure out why is that inventory being held up there, and it's being held up and it's growing, and we're now going into July and it's a month since we started.

And let's try to figure out why those batches are sitting there, and so let's go and figure out what's happening that might make them sit there. And you would go inside, and you'll find that there is an exception here that's waiting to be decided on, and unless that information

process can end up with a result, the physical processes are all waiting for the information process because they have been disconnected.

There's a technology opportunity here that has not been addressed. Why? Because it's so difficult to talk about. Exception represents what we didn't necessarily know, what happened that we didn't anticipate, what happened that may be different from what we thought should happen for the next 12 years, and now you have two multiple organizations getting together, saying, "What should I do? Where should I sign? Who should sign, and how long should it take?"

And where the information is not necessarily there, it's difficult to do. There are legal, social, political consequences. What do we do? We wait, and waiting costs money. It costs money because I'm going to have to find out a few months later what I did and how to connect these two things, and that's the finished goods inventory, tracking up.

And if you were to now say, "What is the

finished goods inventory," you will see a huge number. They are waiting for the decisions. Not only are you waiting for the decision on that, but you're waiting for the batches soon after that, because you want to be confirmed about why there was an exception.

So this would be the third technology, and the result of this is a capacity utilization that is extremely low. I would say that many of the numbers that were discussed in the section before us are really not that far away from reality.

We have to find a way to remember and agree that we really make two products: a physical product which is a tablet or a capsule that has great cost benefit to society and is used for patients, and I think that's one of the greatest things that the pharmaceutical industry has ever done. It's much better than all the other alternatives.

But we make another product, a so-called documentation, information product, and that second product has its primary customer, we think, for the

FDA, but it has a lot of information and a basis to look at exceptions. And I think working together with the FDA around that technology, I think can fundamentally change pharmaceutical manufacturing as well.

Coming to the end of my talk, I said we got together, said we want to find a way to win, and we had a large number of vice presidents who decided that there was a way out. We've looked at technologies for all the aspects that I've told you about. We've carried out different aspects of these technologies in different places for different products, in different parts of the product life cycle, and we've got some really exciting data, and we've called this initiative Continuous Quality Verification.

And we say that we have many pieces of the puzzle that we think can become part of a transformation of this industry. We have got an understanding of the needs. We have some of the best universities in place. We have presented this to the Division of Pharmaceutical Sciences and the

Advisory Board. We have got a very favorable response. We have now talked within CDER to a number of people. We have gotten really excited.

If you remember, I showed you that slide that said, "We want to talk to the FDA at some time." In the last three or four months we've been talking a lot, and we've been very impressed with the openness and the awareness and the good intentions of the people that we've talked to. This is today. This is the Science Board. And as we go past this and we go forward, somewhere along the way we want to be able to also talk to the investigators who might be behind the curve in some of the new technologies.

And this is where we're headed. To summarize, we think technology, when you come back to science, understanding of the needs, we have put together a place where it could be a huge win for the industry, the FDA, and society. But we can only capture this potential if we win together, and we really mean it. And I think if we don't, we're all going to lose, and it's very, very likely that

if we leave any one of the wins-wins out of the three wins, that we will be doing this and saying the same things 50 years from now. Let's find a way to all win.

Acknowledgements: The consortium itself; two colleagues of mine, Professor Charles Cooney and Professor Steven Byrn. And particularly relevant for a presentation such as this, these are my personal opinions and nobody is liable for them except me. Thanks.

DR. WOODCOCK: Thank you very much. I think I'll turn it back over to the Chair for a break.

CHAIRMAN LANGER: How long a break would you like? 10 minutes, 15?

DR. WOODCOCK: Ten minutes.

CHAIRMAN LANGER: Why don't we take a 10-minute break, then?

DR. WOODCOCK: Thank you.

[Recess.]

CHAIRMAN LANGER: If everyone would be seated, we'll get started again.

DR. WOODCOCK: Our next speakers are from the industrial sector. Dr. Norman Winskill and Dr. Steve Hammond are going to be talking about quality regulation from the pharmaceutical manufacturer's perspective.

DR. WINSKILL: Good morning, everyone, and thank you, Janet. It's a pleasure to be here this morning to give you an industrial perspective on what I think is a very important and a very timely topic.

As you can see from the slide and as Janet mentioned, we have a double act from Pfizer. I'm Norman Winskill. I'm going to be followed by Steve Hammond. We're going to share the presentation between us. One of us is a pharmaceutical technology expert and the other one isn't, and I'm the other one.

[Laughter.]

I'm not interested in the technology per se. I'm interested in what the technology can do for me. So I'm going to try and explain a little bit of that, and Steve will concentrate on the

technology itself, and then we'll come back together and see how we put the two together.

So, just running through the order of what we'd like to cover--actually we have the wrong presentation up here, I think. Do you have another presentation that we--

DR. WOODCOCK: A shorter one?

DR. WINSKILL: The title is right, but there was a long version and a shorter version. Sorry, you'll have to give us a moment or two. We have to switch computers.

CHAIRMAN LANGER: While this is happening, are there any questions anyone wants to ask?

DR. WOODCOCK: David Feigal had some information on recalls in the device sector that might be germane to this.

DR. FEIGAL: One of the questions that was asked before is, how many recalls are there? And in the device area there are about 1,000 recalls a year, so if you figure there's approximately 200 business days in a year, that's about five recalls of products per day.

There's about 80,000 products on the market, or 80,000 actually types of products on the market, so if you look at the number of products newly approved each year, which is sort of another sort of metric, there are about 7,000 products approved each year. So it really isn't anything that approaches 6 sigma, if you do the math.

Now, many of the recalls actually probably have more economic consequences for the company than public health impact. About half of them are the lowest class recall, where there is something about the packaging or the labeling or some other type of issue that is a significant cost to the manufacturer but there's no health risk associated with the problem.

But there have been some fairly important recalls that actually happened due to manufacturing problems in the device area this year. Probably one that's still getting quite a bit of publication is the Salzer hip implant, which actually threatens the viability of that whole division of that company, which I think the company's theory still

is that that was a problem with leaving a bit of residual oil on the surface of the hip implant so it didn't seat properly and it would loosen, and that has been a problem.

But there also has been a worldwide recall of ceramic hips, which fractured when there was a change in the manufacturing method, in the type of firing and heating of the ceramic material. So, although most of the recalls are in that low-risk category, there are important examples of products that are recalled where there really are not only quality problems but there are health implications for the patients, as well.

DR. WOODCOCK: Other questions?

Are you about ready to go?

DR. WINSKILL: Yes, we're ready. Sorry about the delay.

So what we'd like to do in the next 25 minutes or so is give you a very brief history of the evolution of process analytic technology--I'll refer to it as PAT quite often--and also our vision for the future. I'll then hand over to Steve, who

will describe some of the specific applications that are of interest to us right now and how we might use those to improve our process knowledge and control of our processes. I'll then come back and describe how we might introduce some of those technologies or how we might now introduce them, and what sort of environment we could create to make sure that we do introduce them appropriately and use them appropriately, and that's referred to as "the win-win scenario," and I'll describe what that is.

So first a quick overview of the evolution of this technology within Pfizer. A lot of the examples I will use are obviously taken from Pfizer. I decided to use specific examples rather than hypotheticals because I think they illustrate the point. I don't apologize for using Pfizer examples. I think it is essential and probably necessary to see specifics, but I don't try to claim that what we are doing is anything different from what a lot of our colleagues in the industry are doing, and I think it's fairly representative.

But rather than hypotheticals, I decided to use specifics.

We started looking a process analytical technology, particularly near infrared and mass spectroscopy, in the mid-'80s, early to mid-'80s, and we were looking at control of fermentation processes. That proved very useful, and we quickly developed and applied the techniques to other processes, particularly near infrared. So in the middle to late '80s we expanded the use of near infrared to synthesis operations, raw materials, packaging operations.

And at this point the application in drug product manufacture, which is what we'll focus on mostly today, was really for a troubleshooting mode. However, in using it for troubleshooting, we found it gave us an awful lot of information we didn't previously have and that conventional tests didn't have.

So at the beginning of '90 we created a dedicated group--and we called it the NIR Group, and it was headed by Steve, who is coming up next--

specifically to spread the word and to develop applications and put them into our processes to enhance process knowledge. And so that dedicated group was formed.

At that point in time it was very difficult to go and buy instruments off the shelf and apply them to the production plant, so a lot of what the group did was develop--not only work with vendors on the instrumentation, but work on a lot of the engineering solutions like sample presentation, automation, and robotics, and that was essential to enable us to put near infrared and other techniques into the drug product plants. We did that in quite a big way in the early '90s. I think I'll show you some of the applications that have ensued from that.

Later, and probably for the last five or six years, I think, other techniques have emerged. Near infrared is still important, but as others speak, as they have emphasized, it's not just near infrared. It's not a panacea. So LIF, mid-IR, acoustic, and a whole range of other, Raman

techniques, are now being studied and they are increasingly being applied.

So, given that evolution, where are we today? And this is just a summary of some of the applications that we have in commercial use on our drug product plants around the world, and it's in chronological order, and you can see that we are using it actually in a commercial environment, everywhere from the beginning of the process, raw material testing and release, evaluation of packaging components, blending, tableting, encapsulation, tablet coating, packaged product. We can actually scan tablets in a blister pack, not just to make sure that the tablets are present, but we run a spectrum on the tablet to make sure it's the right tablet in the right pack. So quite an extensive use, and then at the end of the process we use different process analytical technologies to help with cleaning verification, to ensure everything is ready for the next step.

There's a footnote at the bottom I think that has been referred to. Janet referred to it at

the beginning. Interestingly, I think there are over 30 discreet applications in use around the world, very few in the U.S., less than 15 percent.

And I think that's not atypical of novel technologies in general. Process analytical technologies is a model, but I think if you take any of the new technologies we've looked at-- microwave drying, automated guided vehicles, you name it--it tends to be evaluated and implemented and shaken down overseas, and it takes a long time before that technology is then brought back into the U.S. or used to make products for the U.S. market. And I think a key question is, why is that? Is that the right environment? And if it's not, change it. So we'll talk a little bit about that.

So that was the current state of process analytical technology. What does the future hold? Now, this is obviously a personal vision, and the future for me is about 5 to 10 years in this example, but I think we will see a significant increase in the number of applications. I think we

will see a broadening of the type of applications-- Raman, light-induced fluorescence, etcetera. Acoustical is increasingly used to hear what's going on in the processes, gives a lot of information.

I think what we will see, and what will help spread this technology throughout the industry, is the availability of off-the-shelf solutions from vendors. Right now a lot of us have to develop our own engineering solutions, and go in and, like G.K. showed, adapt them onto blenders to use them. I think that within five years we'll see them being offered by the equipment manufacturers as an option, and that will increase the utilization tremendously.

The other thing I think we'll see, what I described on the previous slide was a lot of individual steps that are being controlled. I think where we are going to is to see all of those steps integrated so we control the whole process. Instead of doing conventional control up to one step, and then we have a nice process analytical

technology on-line to control, for example, blending, and then we take it back into lab-based testing for the rest of the process, we'll integrate the process from cradle to grave, so it can operate at a fast cycle time with tremendous process knowledge which we don't have today.

So our vision of the future is--and this is a pictorial representation of what others have described--moving away from discrete unit operations with laboratory-based testing at the end of each step. And the reason we often wait for that laboratory testing is that if we proceed to the next step--which we can do, there is no regulatory reason why we have to wait for the result to proceed to the next step--but if that laboratory result comes back, and it's our only information today, if it comes back and says there is something wrong with the blend, it's not uniform, if we've taken it through to a tablet, there's a huge cost involved in having to go back and reprocess that, or if there's no rework option, throwing it away. That's the scrap. So it's risk

management that forces the long cycle times and the discrete unit operations with lab-based testing at the end of each, not regulatory.

Where we want to get to, and the vision for the future, is what I think G.K. called continuous process verification: continuous, more frequent, more meaningful on-line analysis at every step of the process, so we can proceed to the next step of the process knowing that what we did before was compliant and of correct quality. We don't have to wait six hours for a lab-based assay. And that is the sort of manufacturing paradigm that we're trying to evolve to in the not-too-distant future.

What are the challenges in getting there? Some of them of course are technical. However, I think the progress that we have seen, and Steve will describe a little bit, is sufficient that it really is not a significant barrier at this point in time. Technical issues can be overcome.

We have made considerable progress in the areas of chemometrics, robotics, the

industrialization of instrumentation. Yes, there are still some opportunities, and probably more significantly I think in the development of faster, smaller, cheaper instruments, so they can be put in more places more often, and probably still some work to be done on the sample interface, how the instrument interfaces with the sample, and how that can be an off-the-shelf solution.

But I think there are solutions to those, and I think that's not a hinderance right now to the widespread application and moving towards the paradigm I described on the previous slide. And maybe the major hurdle for the U.S. right now is the real or perceived regulatory hurdle, and maybe it is more perceived than real, and we'll come back to that at the end.

At this point I'd like to hand over to Steve, who will describe some of the particular applications of interest, or the ones that we are particularly interested in, and then we will come back and talk about implementation.

MR. HAMMOND: Thank you, Norman.

I just briefly want to go through three examples of where installing PAT, this is being driven, the latest advances in this are being driven by a new potent API that we're dealing with, and we've had to look at systems that are totally automated and work in a containment facility where just can't have plant operators even sampling blenders or even sampling off the tablet presses. So we developed a system, and I'm going to start with on-line blending, we developed a system that uses a battery-powered radio communicating spectrometer. It's very small, fast diode array instrument. We actually mount this on the moving blender. We control it and collect data from it remotely in another room.

This is a schematic of the installation that we've just finished performing in our plant in Brooklyn, in New York. The blender is contained in a separate room. There are two containment barriers you have to go through to get into that room. So we have the NIR mounted actually on the blender in a separate room, and our PC controlling

that system is actually out in the corridor in this instance. When this gets to a full manufacturing plant, there will actually be a containment area again for the blender, and the control of it will be in a specialist control room adjacent to that particular room.

For this example I'm going to show you now, the point is that the PC driving the spectrometer and where the data processing is done is some 25 feet away from the blender in another room. This is what the full GMP installation looks like, and you can see that there are two blue boxes actually mounted on the blender. So everything that's back to the right-hand side of those two blue boxes is stationary. What's to the left of the two blue boxes all rotates.

The top box is actually the box that contains the battery and radio-communicating modems. They are what is sending the spectra, once we have collected them, back out to the PC which is outside the room. The bottom box, the bottom blue box, the smaller of the two, is actually the

spectrometer. It's a solid state instrument, so it can be put up with being spun round as the blender moves.

The business end of this is actually the thing that looks like a black cylinder on the bottom of the bin, that's actually shining the infrared light through a window we put into the lid of the IBC, and it's collecting spectra when the bin is inverted. We have some gravity switches that only fire the spectrometer when we know the blend has fallen down against the sapphire window mounted in the lid. The spectrum is collected with the fiberoptic that goes from that reading head on the bottom of the bed back up to the spectrometer.

Now, Norman talked a little bit about the design of the sample interfaces, and with this particular application it's very important, because what we need to do is to collect the spectrum from a known amount of material, and that amount of material must be something that is, in terms of unit dose, reasonable. So we've done a lot of work in designing this reading head, that we collect the

spectrum of between 200 and 300 milligrams of sample. We've done a lot of work in looking at depth of penetration, density of the blends, and how much sample actually contributes to the spectrum.

I've seen a lot of publications recently on doing on-line blend analysis using near infrared, but this fundamental thing of how much sample actually contributes to the spectrum is critical in getting these systems to work and give you realistic answers that you can match to off-line HPLC, and the design of this head allows us to do that. We illuminate an area of some 3 centimeters, a circle 3 centimeters across, with the right intensity to get depth of penetration of about half a millimeter, and we know we collect information from the whole of that sample. So it's very controlled in how many unit dose weights are we seeing.

The sort of information that we're looking to get, the plot on the left shows you the near infrared spectrum of ingredients in a simulated

blend that we used to commission this piece of equipment. We couldn't actually use the active because it is a Class V material, so we substituted that with saccharin, which is innocuous but has the right sort of near infrared spectrum to compare to the active we would have used.

What you can see here on the left is the spectra of those pure ingredients that we scanned before we started the exercise. The change in pattern you see on the right is the movement in the spectrum of saccharin at a specific aromatic absorption for that molecule. That is what we try to do, we find specific absorptions for these molecules and watch the movement at those specific absorptions, so we can track just that one ingredient.

But we don't just focus on the active, we focus on every ingredient in the blend. We look for the specific parts of the spectrum where the movements are really reflecting that ingredient in the blend. So as we run the blender--and this is the first stage of the exercise that we did, this

ran for 15 minutes--we can track the change in absorbance for each ingredient.

And there I'm showing you the change in absorbance of saccharin, which was our active in this case, and lactose and Avicel, two other ingredients in that mixture. So we can track this. As the curve comes down to the bottom and we finally flatten out, we know we've reached the end point of blending, but we can watch the end point of blending for the active and for the other two ingredients in that blend.

Now, to turn that into the normal sort of measurement that we would look to make on a blend, content uniformity, what we do is to take the spectra we collect in groups. The blender was actually rotating at eight revolutions per minute, so what we've done is collect eight revolutions, or the spectra we collected from eight revolutions together, and then calculate a variance across those eight points.

And this is mimicking taking eight samples from the blender into a laboratory, doing HPLC

analysis on them, and calculating the content uniformity. So this is a variance measure, so the Y axis is the variance across eight scans. Along the bottom we're plotting time. So what we can see is the movement in essentially content uniformity for the ingredients in that blend, but not just the active, all of the ingredients.

There's one big advantage to this technology. It is gaining more and more process understanding. The other things that have been talked about, cycle time, are obviously of value, but one of the big attributes of this is the amounts of process understanding that you can get, and plotting the uniformity of all ingredients in a blend is one of the key gains in this sort of technology.

And really to illustrate that, I want to show you the second step in our blending. Once we had blended the main ingredients, we did the normal thing you would do, which is then to add a lubricant, and we blended that. What you see here is the change in uniformity of the lubricant as

it's added to the second stage of the blend.

So with this system we can, in real time, watch the mixing of all the ingredients, look to see when the blending is done, and for the high potency--the product we have to make in a containment facility, we will develop specifications for the amounts of variation that we will allow in the spectra, and that will be validated against conventional HPLC measurements.

The value to us in that on-line blending system, where we have a new product that must be made in a containment facility, the major benefit is no operator contact. Robots will load the bins into the blending area. the near infrared will be placed onto the bin using robotics. Measurements of blend uniformity will be performed in that room, but the data will be transmitted into a control room, so we can avoid operator contact with that product altogether.

There are other benefits. There is no sampling, there is no sample thief error. We get real-time information, which can help recycle

times. We get these multi-ingredient uniformity measurements. We gain a lot in process understanding. We can actually fingerprint the process. We know that those curves I showed you, you can actually change them by the order in which you load the bin, so we can fingerprint even the way that you load the bin and what impact that has on blending. And what this really comes down to in the end is the objective to go to "right first time" manufacturing.

I just want to now show you the sorts of things that we're doing with tablet core analysis because, as Norman said, we're trying to look at cradle-to-grave control of the manufacturing process, and one of the key steps is obviously monitoring what you're doing when you're making or pressing tablet cores.

This really started in an at-line situation in our manufacturing plant in Australia. These people you see there are the plant operators, and they are people that have been using near infrared in that production plant to look at tablet

cores and actually at-line, looking at blends as well.

What I want to focus on is the fact that about once an hour those operators go to the tablet press and they take a handful of tablets. They go to the near infrared and they test content uniformity and potency of those tablets. They do that by passing near infrared through the tablet as a bulk measurement, which means that we do capture everything that's in that tablet and we're not subject to variation at the surface, which can be a problem in some measurements. So we see everything there is to see in that tablet.

Just to illustrate the information value of that, this is a product that was manufactured in the Australian plant, and the conventional analysis suggested there was a problem with blend segregation, maybe, during the process. Using near infrared and looking at 300 tablets across that batch, rather than just 10 tablet as we would conventionally test, allowed us to pinpoint exactly at what point in that batch there was a problem,

and then it became very simple to cure it because it was just a transfer chute that was causing some segregation in the blend. But the extra information that you get from using these sorts of technologies to get analysis of 300 tablets a batch rather than just 10 or 20, really allows you to get to grips with that sort of issue very quickly.

The at-line system I've shown you is fine for most of our products, but with this high potency product that we're going to introduce, we needed to take that further, and we've needed to automate that near infrared testing. And what we've done now is to design this unit, which actually takes the conventional weight, thickness, and hardness modules that are very often at the side of a tablet press, and then introduces near infrared transmission capability into the unit as well.

So tablets feed into this box, they are weighed, they are scanned on the near infrared, and then they go back to be measured for thickness and hardness. And this is actually at the tablet

press. It's fully automated. We're actually having two companies make one half each of this device. Bruker are doing the near infrared side of this instrument, and a company called Schleuniger Pharmatron from Switzerland are making the other half of it. But it is to be a totally integrated device.

I just want to show you some of the spectra behind using a device like that. This is actually spectra of this new high potency product that we have. The black line that you can see there is a placebo tablet, and then the colored spectra are tablets of different strength of that product. So you can see that we have specific information about the active if it's present in that product, and changes in concentration that we can actually measure from that spectral information.

We can use that spectral information to compare HPLC values for single tablets against the value that we would get from the near infrared based on the spectral change that we see. And what

I'm showing you there is the correlation between spectral information and HPLC, but what I want you to note is the concentration in that product. This is from .1 percent to 2 percent, so this measurement is extremely sensitive if it's set up correctly.

I want to finish by describing some work that we've been doing introducing microscopy to look at pharmaceutical formulations. What I'm talking about here is to look at a blend, but not as a bulk measurement, but actually to get in there and have a look at the matrix of the blend close up, and to do the same with a tablet, to get in and actually look at how each of the ingredients are lying alongside each other, and how do we actually make a tablet matrix.

The way we do this is to take an area of a tablet, usually about 2 millimeters by 2 millimeters, we take each of the pure ingredients that we manufacture the tablet from, and we collect their spectrum and we file that into the computer, so we have the spectrum of each pure ingredient.

And then that 2 millimeter area of the tablet, we divide it into squares, usually around 10 microns by 10 microns, and we use a microscope to collect a spectrum from a minute piece of that data matrix. So each square is scanned in turn, each square of about 10 microns, and we collect a spectrum of that square using a microscope. Then we match the spectrum that we get for each square against the spectrum of the pure ingredients.

So what we can do is to take each square and color it in. If we find the active, we usually color it red. If we find Avicel, we'll usually color it blue. Disintegrants, we usually color them green. But we can build up a color map of the matrix of the tablet at a microscopic level.

This is just one illustration of the sorts of information that you can get from doing that. This is an example of two blends of the same product. One blend would flow correctly into the encapsulation machine; the other blend would not flow correctly. The microscopy information revealed that in fact our lubricant was clumped in

the bad-flowing blend and nicely distributed in the well-flowing blend.

In fact, it was interesting, the plant manager when we showed him this information said, "Yes, that's exactly what I thought it was." But at least you can go back and get good scientific data on exactly what is causing that sort of problem, using microscopy.

Here is another illustration of a product that occasionally suffers sticking problems on the tablet press. We analyzed matrix using microscopy. You can see there is a big difference in the way that that tablet matrix is actually sticking together. And what I'm showing you here is the mixing of an inorganic diluent with one of the carbohydrates that goes into that formulation.

In fact, what microscopy has shown us is, if those two ingredients mix together really well, we actually get a slightly weaker tablet that has a tendency to stick to the tablet presses. In fact, you can track back and explain what that difference is. It's a difference in the particle size of the

sugar, the carbohydrate that's fed into the process. By controlling that particle size well, you can avoid this problem, but only after you got the information to explain what the problem was could you go back and cure it, and microscopy really has an enormously powerful contribution to make to explaining process problems.

Up to now, getting that sort of data has taken a long time. Most of the maps I've shown you, our spectrometer and microscope have to work very hard for up to 24 hours to make those maps, because there are about 8,000 spectra in each of the maps. But just recently imaging systems have started to appear that can actually collect the same information in about 10 minutes.

We're hoping within a few years to get these systems so fast that we could take the spectrometer I showed you on the on-line blending system off, and actually put an imaging camera there in place, so we could image the blend as it's mixing. And the sort of information that we should get from doing that should improve our process

knowledge orders of magnitude beyond where it is at the moment.

I'm now going to hand back to Norman.

DR. WINSKILL: I'll finish up very quickly here, but I hope you got a sense from what Steve has described, that we are quite excited by the additional information we can obtain on our manufacturing processes if we can get this technology into the plant routinely. And we think we can, and we think it can be part of the vision I described earlier.

Certainly the technical challenges I think we can overcome. I think what might influence the speed at which it's rolled out and the general acceptability of the technology might be the real or perceived regulatory hurdles. And history has taught us over these last 10 or 15 years generally about the introduction of technology, that it may not be as smooth as we would like to see it.

In fact, I'm going to describe three possible scenarios, all real life examples that we've lived through. One I will call the "don't

use" scenario. The "don't use" scenario is a worst case.

These technologies are not used or developed during the product development basically because of our fear of delays in the regulatory approval. We don't want to put novel technologies into an NDA.

Once we've transferred a process with its controls into production, there may be a tendency not to want to "waste" resources to develop duplicate methodologies and controls when the existing ones work okay.

And, quite frankly, there may be a concern on our behalf of raising the bar. The more information that's available on a process could possibly be used inappropriately against us, and that's a genuine concern.

The problem with that is, if that leads to the technology not being used, I think we all lose. And there is a whole body of information that's just going to remain unavailable to anyone, and that's not a healthy situation.

But again, I said I would use real-life examples. This is a real-life example of "don't use." It's taken from one of our recent products. It's an antifungal polymorph. Conformation for this product was key to the product attributes. During the development, we developed and looked at two different methodologies to conform, to confirm the polymorph, powder x-ray diffraction, obviously a well-established technique but not common on our manufacturing plants to QC labs, didn't exist at the site of manufacture. So the only way to confirm the right polymorph was to send a sample 3,500 miles and then wait about a week for the result to come back.

We developed an alternative, near infrared, common in the lab, available at the site. We could get results within minutes, but it wasn't a standard technique for polymorph conformation. Our initial draft of the NDA included both methods, but our fears and our conservatism made us take the near infrared out of the NDA because we were fearful of questions and delays, and so right now

we have the method on the left, and we send samples across the Atlantic, and we don't use near infrared, not a very healthy situation.

The second scenario is "don't tell." Under this, we want the information so much, we use it but we don't register it and we don't openly talk about it. So we have one set of methodologies that are in the files, and these are used for regulatory approval, and we conform to the specs, we conform to the dossiers. But in addition to that, and in addition, not instead of, we use all these model techniques in parallel, and really we operate in two parallel universes. We have a regulatory universe with old-fashioned conventional technologies. We have another universe that really is the one that counts, but we are afraid to share it.

Another real-life example, and this goes back to, I started life with Pfizer more than 25 years ago in the fermentation area. That's where a lot of the near infrared came from. On the left, you don't need to read that, it's an eye test, but

on the left there's three or four registration specifications and control methods which are fairly conventional, lab-based assays, 12-hour turn round time, and that is still the case.

Today that's the registration method, but over 20 years we've developed a whole set of advanced near infrared, mass spectroscopy, and probes, on-line probes that we really use to control the process. And basically we, as I say, operate in a parallel universe.

The conventional methods work. They give product that will conform and is fit for its intended use. There's no question about that, and then final end product testing is the gatekeeper to make sure of that. But it's inefficient, and really the advanced control and the reason we are prepared to duplicate the universe is, we get much better batch-to-batch consistency, less impurities, fewer byproducts, less rework, etcetera, etcetera, all the advantages we talked about earlier.

We could take this slide from this example and, I think, apply it to today's situation for

drug product manufacture. I think the universe for fermentation control has evolved significantly from a black box art 20 years ago, to a very highly controlled environment with dual networks and advanced computer control, using this information to give us assurance of quality.

We're nowhere near there on drug product, but we could be. And we have to find the right environment to get there, and I think if we could, that's the win-win situation we're talking about. So that's a description of the win-win situation. I mean, we don't need to do the parallel universe and the duplicate testing.

What will it take to get there? I think basically it will take an environment in which the methodology is understood and accepted by regulators and industry alike. We have the same information, the same concerns. We see the same opportunities around the use and application of this technology.

We are certainly not there yet. I think we're making a lot of progress, and I think today's

meeting is a good example of that, but we have a little way to go. And really what we're trying to do in this is, we're dealing with, we're removing the real or the perceived regulatory hurdles.

And I think to do that, we need--and these are personal suggestions on how we can create that environment--I think joint forums to openly discuss the technology and openly discuss the issues and concerns and describe the technology, I think goes a long way. And I know Dr. Hussain, Ajaz Hussain and others, have believed very strongly in this and are starting to do that, and that's encouraging.

I think we need to create an effective process to evaluate these technologies, for example, PAT. And part of that, I think, and maybe the root of it, is appropriate guidelines for the development, for the implementation and the validation of these methods, scientific-based guidelines that we can follow and we can understand, and then you can measure us against. Absent that, it's down to personal interpretation, and that's where our perceived fears come into how

it might be interpreted differently by different people.

How can we do that? Well, obviously we can sponsor joint forums, I would suggest industry/FDA forums, to work up some guidelines. I think we have to recognize that process analytical technology is different from lab technology, and you have different expertise that need to be at the table to develop those guidelines, people from the process control, instrumentation side of the industry.

Another suggestion is to participate in "dummy runs." We have introduced a lot of these technologies. We don't do so without appropriate internal controls for development and validation and implementation, and we have them. We have SOPs for all of that. Like I say, we don't share them because it's a parallel universe in most cases, but we would be willing to share them, and we would be willing to make some dummy submissions. We will submit some methods that we've developed to see what you think of them. We will submit the

controls and the methodology and the SOPs we have used, to see what you think of those.

Quite frankly, I call it "dummy" because we will submit things that are not linked to an NDA approval, so there is less risk for us, and probably that is a way to create a win-win situation. If that helps to evolve to a set of guidelines that we can all understand quickly, then I think we'll be better off.

And then finally I think what's important to us, probably to all of us, is consistent use of those guidelines not only by Center but by field investigators, and that will remove an additional concern that we may get approved but we may get additional questions and a different interpretation of the technology on an investigation. And a set of guidelines that we can all--a bible, if you like--that tells us how to do it, that we can all refer to, and refer to the same chapters in the book, I think will go a long way to remove those perceived concepts.

So, thank you.

DR. WOODCOCK: Thank you very much. I appreciate Pfizer's willingness to come and talk about these things.

The next speaker, who will speak fairly briefly, is Dr. Ajaz Hussain from the FDA, and he'll give the FDA's perspective and some ways that we perceive we could move forward on this, and then we'll try to save enough time for discussion and questions.

DR. HUSSAIN: Thanks, Janet. I did have an extensive presentation, but to the time, I'm going to cut back. But when I sort of put together that presentation, I thought I would have to defend an FDA position: Why do we require product tests, and so forth? But in many ways I think the case has been made by others, and I'll use an example to illustrate some of the challenges from an FDA perspective, and then follow up with a set of steps that we have taken and we are planning to take, and then pose the question Dr. Woodcock posed to you at the beginning of the presentation.

One aspect which I just want to share with

you is, why did everybody talk about blending? It's mixing of powders. I mean, it's at least a 150-year-old technology. But for last 10 years we have been debating that, industry, FDA, so extensively, we probably have spent millions of dollars just talking about it in workshops and so forth. That illustrates in my mind the state of the manufacturing today. That's not the only unit operation. There are a number of more complex unit operations that we have to deal with, but we are stuck on blending. And so that is the situation from my perspective.

Please pardon me. I'm going to skip through some of the slides and get to the most important ones which I want to make some points on. The original outline I had was to just redefine the emerging regulatory issues, share with you my perspective, FDA perspective, look at the problems, and see how we can proceed from here.

The main issue here is that science and technology is progressing rapidly. It is, in fact technology is not a problem right now. I think

getting it into practice is.

Just to reemphasize, I think the discussion topic on process analytical technology, we use that as a model and initial focus point to facilitate discussion on emerging regulatory science issues in manufacturing in general, so that was a model. People have talked about near infrared and other vibrational spectroscopy methods. Again, as a case study, there are many different technologies, any different tools, and not discussing those here doesn't mean we are not considering those.

I think one major issue I think in my mind is why is FDA leading this effort. But when we started talking about this, the reactions that we received from industries, "You're going to do what? This is not FDA's role." But we felt it is, and think we have to take the lead. If we don't do that, we get blamed for it. I think the one aspect we keep hearing is, we are the hurdles, and I think our perspective is, we don't need to--we are not, and we don't want to be. So how do we move

forward?

So just to summarize, we have heard before industry is hesitant to introduce process analytical technology in the U.S. They have done it in Australia. They have done it in other places. It's in practice. Not in the U.S. The points that are made is regulatory uncertainty, risk. That leads to "don't tell" or "don't use" practice. I translate that into uncertainty or lack of understanding or knowledge of how FDA would assess that, as new technology leads to new questions. These questions would be in method suitability, chemometrics. This is status of pattern recognition and validation of that.

The other concern we hear is, old product plus new technology leads to new regulatory concerns which could be added burden, so how to do you deal with that? And clearly a mind set: Why change? One contributing factor to that is, this, when we bring it to FDA, will become an additional test. We'll be asked to do the old method and the new method.

And so those are some of the concerns that we kept hearing, and we said that's not how FDA operates. We are more open to that. Why is this perception out there? And we started talking about this extensively. Clearly we are approaching this from a public health perspective, and to ensure high efficiency of the U.S. pharmaceutical industry from many different views.

Also I think I'm going to start skipping the slides. The point here is, we hesitate to improve or learn about our process during new drug development because we don't have the time. We don't do it after approval.

So when is the right time for process improvement? In some cases, never. We have product, I'll give you an example from a 1997 warning letter. This is a narrow therapeutic index drug which is used in a controlled release formulation. How are we making it? Just read this.

XXX, drug XXX, "time release pellets are prepared by hand-coating powder...This manual

process results in formation of agglomerates and in an accumulation of ingredients on the sides of the coating pan. Operators sporadically scrape this undistributed material...manually breaking up agglomerates...and crushing them during processing." This is, in some cases, the state of the art, not an example that can be generalized, but this is reality.

Clearly, the point has been made that regulatory risk and uncertainty is a hurdle, and we have been working for last several years to remove those hurdles, and there are significant challenges. I was going to talk about the guidances that we have already developed, but let me move on.

The heart of the matter is science. Where is the science in product development? And clearly there are trends where we are going from dosage forms to drug delivery systems to more intelligent drug delivery systems. That is happening, but that has to happen more quickly.

The molecules that we are developing as

drugs are more complex. They need to be managed more carefully. And so design of intelligent drug targeting systems and so forth is happening, but we are still stuck in a 100-year-old technology at the same time. The principles of what we do originated 100 years ago in the art of compounding. In many ways we are still--a lot of those things remain. Most dosage forms are complex multi-factorial systems, yet we treat them as univariant or multi-incident systems where we study them one at a time.

From an FDA perspective, when we have to establish classification, when we have to establish controls, what we face is a high degree of uncertainty on what the impact of independent variables have on performance. So when you want to change something, we have no clue generally what that impact may be, so the additional tests come in.

So not to belabor, not to just harp on that point, I just want to move on, but at very fundamental levels, material science, if you look at polymer science, if you look at all other

fields, do we understand our materials? Not necessarily. In many cases the functional attributes of the materials we use, the ingredients that we mix in a tablet, are not well understood.

The official monographs that we have are focused on chemical identity and purity, and that's probably what it should be. Defining the functionality of an excipient in an official monograph is probably very difficult to do and probably not necessary to do, because when you mix powders, you lose their functionality and you have to really deal with the functionality of that powder mix. So doing things on-line, doing analysis for that mix, is more relevant.

So just I'm going to quickly focus on the current paradigm is testing to document quality, and predominantly with wet chemistry, and that case has been made. But that's not what our FDA policies are. In fact, it's to look at the guidances and, say, the GMP guideline. These are the words that we use. Quality cannot be tested into products, it needs to be built in.

That's what we say, but we do focus on testing. And the main reason for that is, if you want to build quality in, quality has to be built on knowledge, not data, and the level of sophistication and the details that our data can resolve is either medium to low. So we are in the bottom of there, where you're looking at historical trial-and-error data to establish specification and so forth. That is a contributing factor.

We have talked about blending. I'm going to quickly skip through this and say, why are we debating this? What is this debate all about? For 10 years we have debated this, and from an FDA perspective one could argue it's assuring quality. From an industry perspective it's simply to document. There is no quality problem we have to document, and we struggle to document that.

But it is question of representative samples, and it is an indicator of art versus science debate, and is illustrative of test versus control mentality. Blending assay that we do in process is actually a test. You take a sample,

test it. If it's not homogeneous, and if it don't have a protocol for reprocessing, you would throw away that batch. If it was a control, you would blend until it's homogeneous.

Just to illustrate, from an FDA perspective, why we raise some issues here is, how do we control the quality of tablets right now? Suppose you have two steps. You have blending and making a tablet. You would blend, take 10 samples or 6 samples, and if the percent RSD or standard deviation is less than 6 percent, it's homogeneous. Then you would make your tablets. And how many tablets do we test for content uniformity? Ten. If the batch is 10 million, 20 million, that defines what goes up.

And we recently did some research in collaboration under a consortium that we formed, Product Quality Research Institute, and a major company in the industry who did this work for that thing, sent this data to me. And this was a commercial, is a commercial product. They actually did this test to support the research efforts that

FDA is having, and found a problem in a commercial product. And the problem was, those 10 tables were not really, truly indicative. They had to go back and correct that process.

I'm not going to get into how blending is done in chemical engineering. I was planning to do that, but let's skip to certain advantages that we see moving towards PAT. You are shifting the paradigm towards feedback control. You are helping to build quality in by improved and more efficient control of raw materials. You have process data that can be used for scale-up and modeling. Adequacy of mix with respect to all critical components, and Steve Hammond made that point.

And just to illustrate that point, content uniformity is one attribute. Dissolution, drug release, is another attribute. If we do 10 tablet testing for content uniformity for a 10 million batch, we do six tablets for dissolution. Dissolution depends on a number of factors. We do not require content uniformity for critical excipients. You only do for drug.

Here is an example. The person who provided, again, is from a major company. He is in the audience. He didn't want to be named, so I'm not naming him here. This is a situation where we would not even have tested for blend uniformity because the amount of drug is so high, and the tablet was failing, and was failing in dissolution as a function of time.

So if you have 10 million, what happens early part of the run, late part of the run, you might miss that. And new technology--this is from Steve Hammond--can address that.

Something that I just wanted to point out, which is, our experience is slightly different from Steve Hammond. We have been working in our labs with near infrared imaging, and we can actually do image analysis where you're looking at the chemical image, the grey and white spots, so each pixel of that has the complete spectra. And actually we acquire that in less than a minute; he said 10 minutes.

So we can actually look at a tablet, take

a visual picture, and each pixel can give you full information, so non-destructive and so forth. And you could see whether it's uniform or not within a minute, and you can distinguish whether it's not mixed properly and so forth. But the technology is not an issue. We can do this step. That was the only point I was going to make here. And it is a win-win opportunity from public health as well as industry.

And one point that was raised was out of specification and recalls. On the average, I think from a quality reason--not average--last year, the number is in my mind, I don't have an accurate number, we had about 150 recalls due to quality reasons on the drug side. Now, there were more recalls for other reasons, packaging, labeling, and so forth. But in my mind, the number 150 is in my mind, so I'm pretty sure, but that's the score. The large percentage of out of specification recalls are for deviation to the physical attribute changes, and we right now are not focused on physics, we're focused on chemistry.

One win-win situation from a public health perspective is, when somebody wants to go on-line to save money, time, and so forth, to do that you really have to understand your process well. And that is a win-win. You cannot just put something on-line and be happy with it. So it does support development of more robust processes and a high level of process understanding is needed, and that's one win-win that we are.

Let me just quickly go to what we are doing. What should FDA do to facilitate introduction of PAT? Clearly in my mind, in our mind right now is, eliminate regulatory uncertainty. We have stated repeatedly the official FDA position: FDA is a science-based organization. FDA will accept new technology that is based on good science. We have done that repeatedly.

What we don't have right now are standards for PAT, for its suitability, validation, and a whole host of things. In fact, you will have to approach this broadly, and every aspect of the

process, including all of specification, how to deal with, has to be developed. We don't have that. In this regard we probably are lagging behind Australia and other countries, which is a bit unusual, for FDA to lag behind.

What should we do? Just to continue on that. Define a clear, science-based regulatory process. That we feel is important. Current system is "adequate for intended use" would be one part of that. We will have to think about a win-win scenario, and to do that, defining that the current system is adequate, it may not be as efficient as it can be.

So if it allows introduction of new technology without becoming a requirement, we have to think about that. So introduction of PAT, at least for some time, should not be a requirement, would be one approach.

Define conditions under which PAT may replace current "regulatory release testing" is important. Don't simply keep adding the number of tests and hope that helps. You have to give

something up, so you have to balance, based on what is needed, based on the redundancy that is required, balance the number of tests that are required.

We have to develop a clear understanding of how to deal with invisible problems that are not visible today, but will become visible when you have process analytical technology. We will have to have science-based review and inspection practices, and we will have to work towards international harmonization.

Again, the point I'm making here is, generally FDA has led the way in those things. Here, we might be following, and we need to catch up.

So the challenges we have, limited institutional knowledge and experience, we have to work towards building that. Seek input and collaboration, we feel that is the only way right now.

What we have already accomplished is, we discussed this at the Advisory Committee for

Pharmaceutical Science and got strong endorsement from that, and the committee actually recommended that we form a Subcommittee on Process Analytical Technology. The Federal Register notice has been out. End of November is the deadline to apply, and we encourage all of you who are here from industry to consider being part of that subcommittee. It's an open process. And we are going to define the objectives of that committee in terms of defining what the questions are for FDA.

We also think we have to partner with industry, maybe with individual companies through a creator mechanism. Clearly we are already linked to academic pharmaceutical engineering programs and process analytical chemistry programs. We already have a consortium, PQRI, that we are using for that.

So I'll leave it, stop my presentation with the questions Dr. Woodcock raised: Are you able to support what we are trying to do? What resources do you suggest FDA draw on? And are there additional aspects to regulation of product

quality that we should focus on? Thank you.

DR. WOODCOCK: Thank you, and we'll open it, if that's all right with the Chair, we'll open this for discussion now.

CHAIRMAN LANGER: Yes. I would love to get comments from, questions both from our Board as well as anyone in the audience, and particularly, you know, along these lines. Bob?

DR. NEREM: I mean, number one, it seems almost like a no-brainer that this ought to move forward, because it seems like FDA has a mission. Part of its mission is in fact to facilitate the use of advanced technology for the benefit of the American public.

Having said that, what is it in the regulatory process of Australia or of other countries where they have been able to bring this on board, that makes it easier to bring it on board there than here?

DR. WOODCOCK: Yes. Do you want to ask Pfizer?

DR. NEREM: Right.

DR. WOODCOCK: While you're coming up to the mike, let me give a stab at it. I think many of the other countries have less extensively developed regulation in the manufacturing sector, frankly. That makes it more difficult for us to change.

DR. NEREM: Does that suggest that we have too many regulations in the manufacturing sector?

[Laughter.]

MR. HAMMOND: The difference in Australia really was the attitude of the TGA, the regulatory body there. They had an instant interest in the technology, to the point that they didn't just want to hear about it, they actually wanted to touch it.

They came into the Pfizer plant, they brought staff, it was actually other companies, and they played with the equipment. They had heard a lot about it, but actually wanted to see really what it could do, play with it themselves, and went away with their own conclusions about what it could do.

And I think that was the difference, such

an interest, and I have to say Ajaz is treading down the same path. But that was it. It was a real, "Let's get to know this, let's touch it, feel it, play with it."

DR. NEREM: Is Australia the only place where this has happened, or has it also happened in Europe?

MR. HAMMOND: It's happening very quickly now in the U.K. The MCA, with a meeting we had with them in March, they basically said to us, "Well, what's your problem? Why haven't you brought this to us? What are you waiting for? We like it." So it's happening in a number of countries now.

CHAIRMAN LANGER: Yes?

DR. DOYLE: Are these technologies that you have developed in-house, are they proprietaries, so you don't want to share them with the rest of the industry?

MR. HAMMOND: No, it's the exact opposite. In fact, we have developed these with commercial instrument companies, and the only way we can get

those companies to develop these systems with us is to agree that they are available to anybody. That system I have shown you is a part number for Zeiss. If you go to Zeiss and say, "I want," I can't remember what the part number is, but that's what you'll get. It's commercially available.

DR. DOYLE: Well, in the microbiology arena we use the, what, AOAC, the Association of Official Analytical Chemists, to run these, I guess you would say validation studies, to compare to the gold marker. Couldn't something like this be developed?

MR. HAMMOND: Yes, I think it could, and in the U.K. we're doing-we're running a program with the London School of Pharmacy to take these technologies, particularly near infrared, and develop gold standard guidelines on how you would actually set them up and use them. So I think that's a very good idea, yes.

DR. WOODCOCK: The Product Quality Research Institute, which is a foundation, a separate foundation, was set up partly to do this

type of work, which is to collaborate amongst industrial, academic, and regulatory sectors in doing the scientific work to, you know, develop scientific understanding, partly for introduction of new technologies. So there is already an existing mechanism, as Ajaz said, wherein if general kind of work needed to be done, that it could be, that would be generalizable.

CHAIRMAN LANGER: Other questions or comments?

DR. PICKETT: Yes, I just had a question. You know, this is, I would agree it's almost a no-brainer to really try to get this implemented, and one of the issues that I was wondering if it is an issue, is whether or not within the agency, if there is the appropriate scientific expertise in the agency to really begin to address some of these newer technologies as they come on-line.

DR. WOODCOCK: Yes, that's one of the things we wanted to talk to the Board about, actually, because as Ajaz pointed out, much of the emphasis within pharmaceuticals for the last 100

years has been in the wet chemistry laboratory. Much of this is in chemical engineering and mechanical type of sciences and technologies that need to be brought in. And no, we don't have the range of expertise, neither in the field nor within the Center for Drugs, right now.

CHAIRMAN LANGER: Any comments from, we have lots of people in the audience? Yes?

DR. WOLD: I am Svante Wold from Umetrics, Incorporated. We are going to give a brief comment after lunch, but right now, I think that one way to get things rolling, we represent a technology that exists since many years, and one thing I wanted to say is that this technology, the pharmaceutical industry, interestingly, are far behind.

Like the semiconductor industry that was mentioned, they applied this, exactly the same technology, and the semiconductor industry is very much a chemical process industry, which we don't understand what it is. All steps of making chips and wafers and so forth are chemical. So it's very much the same technology, the same instruments,

near infrared is coming, and so forth, and it can just be lifted over.

Now to be lifted over, I think one very interesting initiative would be if FDA and some drug industries agreed, let's set up a feasibility study on some existing processes where the traditional quality control works in a certain way. What will happen if we now put on proper process analysis chemistry and proper multi-variate evaluation and see what happens? And then we would all learn, and hopefully one would see that this is a win-win situation.

CHAIRMAN LANGER: Any other comments? Maybe we could put those three questions up on the board for a second. But I mean the first one basically is, should you go forward, so maybe just to get a consensus. I think we sort of heard it's a no-brainer, but is that a fair sort of preamble to the questions?

"Are we able to support the approach?" So does anybody have any disagreement with that? That's a no-brainer. I think several people said

that.

How about the other two questions? Are there any comments? I mean I guess there were comments kind of made. Are there any particular questions, Janet, that you want people to focus in on?

DR. WOODCOCK: Well, I would appreciate any ideas the members of the Board have about academic, other resources that you know of. Obviously, we are prepared, as we said, to collaborate with the industrial sector on this, as well as the academic sector that we know about, but it strikes me there are many broad areas of expertise that need to be brought into this, as well as we need to hire some broader skill sets within the agency.

And the other part is the additional aspects of regulation. I mean, I think the question that was asked earlier about why haven't we adopted this and so forth, it's hard to recognize, I think, unless you are actually involved in this, what a large paradigm shift this

will be for the method of regulation of product quality, the way it has been.

And we plan to go about this by taking some examples, as the person who just spoke said, taking some pilots and so forth and moving forward on small pieces, but moving to this approach really does pose a lot of challenges for the FDA. I don't want to underestimate that. And I guess those are-

DR. NEREM: Challenges--

DR. WOODCOCK: Pardon me?

DR. NEREM: Challenges because of your mind set or what?

DR. WOODCOCK: Yes, I think that's a fair--well, it's really changing, yes, it's changing the philosophy or the paradigm, okay, from a testing paradigm to a reliance upon physical, chemical, on-line, and other types of trend methodologies, pattern recognition and so forth. It's a very different paradigm.

It's going to cause some disruption to the industry, too, because we're going to find out

stuff, as Ajaz was saying, we're going to find out things about existing products. There are existing products out there in market. We know they have problems. We know they fail their specifications intermittently. We don't know why. Now we're going to find out why.

And so we're going to have a large range of issues that we're going to have to deal with as we go forward on this. But if you all feel, and I see you have some thoughts on this, you ought to share them with us.

CHAIRMAN LANGER: Bob, did you want to share something? Do you want to say something?

DR. NEREM: I want to let Alexa speak. Then I'll share something.

DR. CANADY: As I listen to you, if I were an industry person, I'd be terrified by your attitude. You know, I mean, in a sense of the concept that there's going to be tremendous dislocation. And I guess to me the idea of a successful transition is the avoidance of that dislocation rather than the acceptance of it.

DR. WOODCOCK: Yes, that's a good additional aspect to keep in mind. Obviously, to make this a win-win, we're going to have to avoid those consequences.

DR. NEREM: Yes. I guess, you know, that last question--and obviously I'm not speaking as an industry person--but the word "additional" seems to me not to be the right modifier. Because presumably, you know, if one does a zero base analysis of the process with new technology now in place, you will come up with different regulatory aspects which won't necessarily be additional regulatory aspects.

DR. WOODCOCK: Okay. Well, I wasn't talking about adding regulatory aspects. I was talking about what Dr. Canady was talking about. What are the implications of this are we going to have to be careful about as we move forward?

Obviously, if this is set up in a way that people perceive severe negative consequences from this, that's an additional aspect that we need to keep in mind. I wasn't talking about should we add

more testing. That wasn't the meaning of the question.

CHAIRMAN LANGER: Owen, you wanted to say something?

DR. FENNEMA: Well, I'm a little puzzled about why there's so much concern about the difficulty of executing this kind of an advance. It doesn't seem that difficult to me. Maybe that's--maybe I'm naive about this. I don't know. But it doesn't seem that difficult to me, from FDA's standpoint, to adopt these kinds of new methodologies.

What is needed, I would suggest, is simply a rather short document describing what FDA's expectations are when somebody comes forward with a petition proposing a new methodology. You know, what kind of validation procedures they use, some data they have collected to show that this is effective and accurate and repetitive. That is, to me, not a very difficult thing to do, and it should be done.

CHAIRMAN LANGER: Any other? I'm just

going to make--you know, when you mentioned on the academic thing, one thought that occurred to me was, you know, maybe to give some seminars at universities and chemical engineering schools, and certainly at MIT. Maybe Dr. Raju and I could work on that.

But there's also other schools that we might be able to do that. I mean give, you know, a lecture and a seminar series, I think might, you know, get departments realizing that that would be useful, and maybe some students and post-docs seeing that.

So maybe if you--I'll be happy to help--you could take some initiative to do that at MIT, and maybe Georgia Tech might, you know, and just different schools, there's a lot of chemical engineering departments that are around that might, I think, benefit from that. So that would be a useful way of, you know, maybe trying to sow some seeds.

DR. WOODCOCK: Ajaz?

DR. HUSSAIN: No, I think we are very

cognizant and we are actually working towards that right now, and--

CHAIRMAN LANGER: How?

DR. HUSSAIN: Well, at present, for example, right now I have a faculty appointment at Michigan and Purdue, and we are sort of downlinking University of Michigan pharmaceutical engineering seminars to FDA. We are making presentations on this quite often now.

CHAIRMAN LANGER: Is this just pharmaceutical or--

DR. HUSSAIN: No, the School of Engineering has a pharmaceutical engineering program now.

The point I want to make is, there is a transition. Pharmacy schools have lost the focus in this area, because they--I came from pharmacy school, I was a teacher there--they moved towards clinical, and a hole got left behind. And Rutgers, Michigan, have now a pharmaceutical engineering program in their engineering school. So we are working with them to get our ideas and our needs

expressed, so that as their curriculum develops, as their research programs develop, they keep that in mind. So yes.

CHAIRMAN LANGER: I think that's good, but I think that some of the comments that people in the audience made, as well as here, is that there is a lot of work going on in, say, materials, you know, semiconductors, material science, chemical engineering. And so somehow, again, I think people look for good problems, and this is a good problem. So that may be a very different set of people that you also want to, you know, get acquainted with.

I'm sorry, Bob. Did you want to say something?

DR. NEREM: No, I would just simply, and you probably know chemical engineering better than I do, Bob, but it seems like a number of chemical engineering departments have initiated efforts in industrial bioprocessing. I think that's becoming wider spread than many would think.

CHAIRMAN LANGER: That's right, yes, but I think that some of these particular things, I don't

know that they are necessarily focusing on. So I think it's actually a good point. I think it's actually a natural thing that they would probably be quite interested in this. Yes?

DR. PICKETT: Bob, just another question. I mean, we haven't heard from some of the other division directors, but I would be curious whether or not there's any lessons to be learned here, because some of the other divisions like CBER certainly have receive innovative new products, have had to rapidly accommodate new technologies in order to release those products, and are there things that can be learned from other divisions that would be applicable here?

CHAIRMAN LANGER: Kathy?

DR. ZOON: Again, I think a number of comments were made on the importance of an adequate science base for the agency and supporting the scientific underpinnings, to understand both from a process point of view and an analytical point of view the implementation of those processes into the biopharmaceutical field, for instance, which CBER

primarily deals with.

And one of the aspects is really trying to understand the technology early enough, and right now I think some of the areas that we're trying to focus on really deal with microarray and proteomics and looking at their eventual adaptation to processing of biopharmaceuticals in a way that has a quicker turn-around time and reliability and quantitateness that will be utilized in the future. So I think having the scientific underpinning within the agency is extremely important no matter what discipline in whatever area we have, and each of the different Centers can lead the way for their particular areas of expertise that they may have.

One of the interesting thoughts in hearing the presentations this morning, though, which I see as maybe not so much an FDA willingness to deal with the change, it's actually how willing the broad cross-section of the pharmaceutical industry is in accepting this change, because I think people are in different places. And certainly some of the

older conventional products that have been around a long time, it will not be as easy for people to adapt the technology to those processes, or they may not want to make the investment. And then it becomes, if it becomes the state of the art, then that becomes CGMP, and then how does that relate then to the standard for the industry across different product areas?

I think it's an important discussion, and where we have the capability, I don't think FDA should be the stumbling block for this at all, but I think we do need to investigate in the broader cross-section of the industry where people are in this, and have an understanding. And then how can we help get people into this field, to have better and more consistent products using the technology?

DR. WOODCOCK: Ajaz said this so quickly, I think, that people may have missed it, but I really think that one of the things we will have to do with introduction of this new technology is that it cannot become the new standard against which all else is judged for a very long time, to be fair,

that that be a stumbling block. If three people, three different firms or lines, production lines, have this technology, then that could not be considered the state of the art.

And many of you are not aware of how this usually works, but there is a current Good Manufacturing Practices regulation, and one of those has to do with sort of continuous improvement of the basic standards for manufacturing, and we don't think that should be part of this early implementation.

CHAIRMAN LANGER: Any other comments or questions?

DR. FEIGAL: Could I comment about devices, just very quickly?

CHAIRMAN LANGER: Sure.

DR. FEIGAL: One of the interesting things to consider about devices is that some of the things you can do with pharmaceuticals, such as rely on pharmacology and pharmacokinetics because they are all drugs, you can't do that for devices. They are such a heterogeneous group of products.

And so it's interesting to look at how the structure of the consumer protections were built around devices.

As you are probably aware, the majority of devices are approved with the 510(k) mechanism, by which they show that they are substantially equivalent to another product. There is no manufacturing section in a 510(k) application. The kinds of manufacturing controls that they have to put in place do not get any type of pre-market clearance in that process. There are still manufacturing standards and controls that are required, but they are to be established by the field at the time of the inspection.

So it creates a very different environment that actually allows rapid changes in that kind of a sector, because there is no pre-market clearance, there is no manufacturing supplement, none of those types of features. Now, there are times when that creates a problem, and we have a real concern about the products.

There have been implants, for example,

that have had sort of constantly changing design features in terms of thinness of material, method of casting, which plastics were used as cushions for--it was a weight-bearing implant. And it was very hard to know, as we looked at failures of that implant, what we were dealing with, because there was no requirement for us to be told when all of the different kinds of changes were taking place. And that is, it's actually one of the nuances of the device regulations, is when do you change it enough that you actually owe us another application because now it's a new device?

The 60 or so devices that are novel enough to be approved under the PMA process have similar types of manufacturing requirements, but again because of the fact that devices are so different from each other, I think there probably is a climate where we are much more used to change.

And like drugs, one of the things that Janet mentioned earlier--or I think you did, I can't remember if you did or if this was a discussion on the break with someone else--but one

of the things that has happened is that many more things have moved towards no longer requiring pre-approval from us, but being things that they notify us change is being effected, or things moving into annual reports, or in our case we have something called real-time review which is used in a lot of the manufacturing, manufacturing changes.

But it's actually one of the hardest things for us to know, is when a change enough that you actually should go back and learn something about the product again? It's a big issue for biologics. There are times when a subtle change actually has an unintended disastrous sort of effect. And the hard judgment in science-based regulation is to say which of those make enough difference that you want to see those in advance, want to stop and think about those, versus what happens with many things, including most recalls, which is you discover a problem, you go back and figure out what caused it, and see if you can prevent it the next time around.

CHAIRMAN LANGER: Any others?

DR. FENNEMA: There are some questions in the back.

MR. PARSONS: John Parsons, and I represent Umetrics, but my background is 25 years in the industry from the commercial side. And I would just like to, now that I'm not in the industry, make a comment I think that isn't addressed here.

I think, as I listen to what Ajaz and the group here have presented, it's invaluable to the industry and to patient. I think that's the key here, that we deliver the quality as a commitment to the patients, and obviously that's what the agency is all about.

But from the commercial side I can tell you, as a member of an executive board, this kind of discussion from an investment standpoint and a risk standpoint just turns my stomach, because of the concerns that were expressed before. It's a reengineering effort that has been described by Pfizer, by Norman and Steve, that has to be done through the process change and also all of the

investment in terms of the equipment. And it's also a risk I think that has been identified in terms of what will we find that we didn't know about the product before, particularly for the older products.

I would just say this. I would encourage the agency, as you move forward, that you do this as a cooperative effort with industry, and I am sure that you will do that, so that there is a transition period with the enforcement necessary to bring this to fruition, because it's absolutely necessary, but also where there is a cooperation, so the industry doesn't rise up and with the powers that are there, perhaps interfere with something that's necessary and that absolutely will benefit the patient in the long run. Thank you.

CHAIRMAN LANGER: A comment back there?

MR. ROY: Suva Roy, Otsuka Maryland Research Institute.

Having lived on both sides of the fence, so to speak, being in FDA, being now in industry, I don't think the regulatory hurdle is as big as

people think it is. There is the process of alternate controls that can be applied, and FDA doesn't even need to approve those things. Perhaps what the FDA can do to change that, to make it a formal process, is allow the companies to submit supplement to the application, and allow that for approval which is not a current process that is entertained or used.

And secondly, the other comment I wanted to make is that it is very heartening to see that now, after probably about 25 years after I had played with something, that something else is coming to fruition. Back when I was working in industry, I had worked with, played with, literally with tablet compacts and acoustic vibrations to see if that tablet fractures. However, back in the early '80s there was not enough computer power to do that quickly. As a result, it was just an academic thing, but it is very interesting to see it coming through, and I really, really like to see this develop, and I commend Ajaz for bringing it to the attention. Thank you.

CHAIRMAN LANGER: Any other comments?

Yes?

MR. TURJAC: I had to say something. Emil Turjac. I'm with Purdue Farmer right now, but I've taught and I've been a consultant, and I've been around even longer than the last gentleman, about 30 years.

To our academic friends, I was there early enough, when we tried to introduce HPLC, and the FDA did not have instruments or people who knew how to run it. And as a time-consuming thing, to keep stalling, it was "What's wrong with titrations? They've worked for 40 years," until they could hire the people and get the material.

Having done that, and most of the people of my genre are now directors or the like, and they're sitting back saying, "If we put something new in, it's going to delay our NDA, so let's just go to the USP. We know it's better, and for alternatives we would have like laser light scattering for particle size as our alternate method, and for thermal analysis for melting rings

as an alternate method, because God forbid we hold up, because we've got 15 years of our 17-year patent already shot. We can't have that come back to us."

So I think it's gun-shy. The younger chemists and the younger FDA people are going, "What's wrong?" But the people who make the decisions have been burned and they don't want to do it again.

CHAIRMAN LANGER: Any other comments?
Yes?

DR. HUSSAIN: Just to comment on the alternate approach, the alternate approach is fine. I think that leads to the two parallel universes that Pfizer talked about. You still have the old method that you have to do for regulatory compliance, and then you can have an alternate. It doesn't solve the problem. I think we really have to bring the two universes together.

CHAIRMAN LANGER: Any final comments before we eat?

Well, I think that the consensus is

certainly that everybody seems to think that you should go ahead with this

--oh, is there another, another one?

MR. ROY: I just wanted to add to Ajaz's comment, that if FDA has got a process of approving the alternate methods once they are mature enough and the company wants to do so, that solves the problem. Then it solves the problem of parallel universes. Unfortunately, that's not a process that is right now in place or is actively entertained.

CHAIRMAN LANGER: I think on that note we'll probably adjourn the session and meet back at 1:30, but I think hopefully the dialogue can obviously being continued, and people should feel free to give you feedback, and it will be great to hear in future sessions how this is going, but obviously it's very positive.

DR. WOODCOCK: We thank the Board for their advice.

[Whereupon, at 12:45 p.m., the meeting recessed, to reconvene at 1:30 p.m. the same day.]

AFTERNOON SESSION

CHAIRMAN LANGER: If people could take their seats, we will get started.

A number of people have requested to make comments, so the first one is Dr. Wold and Dr. Parsons and Dr. Josephson from Umetrics. What I was going to do is ask each group to hold their comments to 5 or 10 minutes maximum, but if the first group would like to get started.

DR. KETTANEH-WOLD: I would like to talk a little bit about real quality control of batches as they are evolving, rather than doing what we have talked about, was one waits until a batch is finished, do some quality control, find that it's not up-to-date. You cannot--the accepts are not found, no correction can be done, and you get only scrap.

Instead, one can have real-time quality control. How do we do that? Well, first of all you have to have some infrastructure. That is, on your batch you should be measuring on-line some adequate variable, adequate parameters, like

temperature, pressure, whatever.

We summarize that multivariately in a good way, and model the evolution of the batch, and once we have that, we have good representative set of batches. You can make a fingerprint. That is, you can have the average trace of good batches within three sigma limits.

Once you have that, which is based on modeling the evolution and having this control chart, new batches as they are evolving in the real time are displayed inside this fingerprint, and you can see it. If they go out of the limits, all you have to do is find out which variable is causing that. You can just double click on the software and say, "Why is my batch going out?" And you can make immediate correction.

And not only that, but when the batch has reached 50 percent of the evolution, we can predict what the whole quality will be, and you can see this prediction changing as the batch is evolving. And this is just based on multi-variate analysis and then taking the average and making control

charts.

And here I will show you a blending. This was a pharmaceutical process of mixing, and you can see here the trace, the fingerprint. This is the fingerprint. All good batches should evolve right in this little, little interval. The red line are the three sigma; the green line is the average trace, the golden batch, the average trace of the good batch, and these are two summaries of it.

And you see now a new batch as it is evolving, and you see that there is first a starting phase, then there are levels that are changes of the variables, and then it showed evolving here. This batch has started increasing the level much too early, and if we just double click on that, it tells us which variable has been increased way too fast, and then you can immediately correct and bring this batch back to make it evolve within the limits.

And if you want to see what is the control chart of this variable, you can just double click on the variable. You can see that for this

variable it shows first there at 3,000 something here, and then raised the level, and they have raised the level way too early. And this allows for correction immediately rather than when the batch is finished.

And if you have a lot of these and you follow them, and you know that these batches stay within the limits, you are almost sure to have a good batch. And this is very simple, it's visual, it's based on good science. It uses multi-variate analysis to take all the variables in account, including their correlation. It's like your Dow Jones that's a summary of our stock market. It tries to do the best possible summary of the evolution, and it also takes in account all the raw material and all the initial conditions.

So the benefits are enormous. It brings the analysis of three-batch data to a simple framework. It allows interface as the batch is evolving. You can predict final quality. And it applies to both the evolving batch and the whole batch. The results are very easy to interpret, and

it can facilitate compliance with regulation, because instead of sending numbers, just send the fingerprint.

And one last comment on everything. As somebody once said, that change is the practice complicated and frightening, but not changing is worse. It's just that one has to manage the change with a transition. Thank you.

CHAIRMAN LANGER: Are your colleagues talking, or just yourself?

DR. KETTANEH-WOLD: No, that is--

CHAIRMAN LANGER: Okay, great. Any comments or questions?

Okay, then we'll go on. The next statement and comment will be by Gideon Kantor.

DR. KANTOR: The purpose of this talk is not for you to find out whether I'm ambidextrous. By the way, you need to change gears because you are now going--excuse me, you have the page on that, what I'm going to cover, and it's a little bit of a different topic. And what I'm talking about is enhanced regulation, regulatory science,

for animal research.

First I think I should kind of give you a little bit of a sketch of my qualifications. Okay, what I'm going to talk about is first my qualifications, then I'll talk about the rationale for my proposal, then I'll talk about the enhancement considerations, and then finally one thing I always end up with is final comments.

Okay, my qualifications. I am a past president of the FDA Sigma Xi Chapter. I would like to brag a little bit here. I was the first CDRH president of the FDA Sigma Xi chapter many years before it reached popularity at CDRH. And I am a member of the chapter now.

In 1995 I retired as a research physicist from CDRN/OST, and since then I have regularly taught as Adjunct Associate Professor, Biomedical Engineering Department of Catholic University of America. I have taught a course in neural stimulation in rehabilitation, and I also give some lectures on regulatory aspects. I am trying to teach to the students that really want to go into

biomedical engineering in a practical manner, if they don't like to get involved in regulatory aspects coming up as a part of it, they better change their field.

And I am presently a member of the Institutional Animal Care and Use Committee, and I want to emphasize that my statement below is strictly my own. I would like to reiterate that. My statement is strictly my own. Any members of the committee, in this particular case guilt by association does not apply. But I am mentioning that to the membership of this committee to explain how I developed an interest in the regulatory science issue of enhanced animal research.

Now let me talk about the rationale. The unjustified death of a volunteer at Johns Hopkins Medical Center, and previously the unjustified death of a volunteer at the University of Pennsylvania Medical Center, are of great concern to me. I would like to say why this is of concern to me. I am a product of Hitler Germany, and I do know I exaggerate, but whenever I see what I